

SYNTHESIS OF EPOTHILONES AND RELATED ANALOGS

Cross-Reference to Related Applications

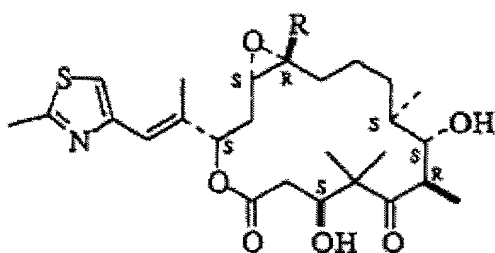
This application claims the benefit of U.S. Provisional Application No. 60/240,488, filed October 13, 2000.

Field of the Invention

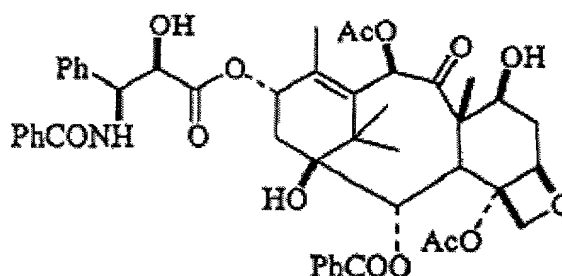
The present application relates to the synthesis of chemical compounds that are useful in treating cancer. More specifically, the present application is directed to methods for synthesizing epothilone compounds and related analogs and derivatives thereof. The present application is also directed to chemical compounds, and pharmaceuticals prepared therewith, formed through the methods of the present invention.

Background of the Invention

Two unique macrolactones were detected during mass screening for Taxol-like substances by both Merck Research Labs and the GBF (Gesellschaft für Biotechnologische Forschung mbH, Germany). Bollag, D.M., *et al.*, *Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action*. Cancer Res., 1995. **55**(11): p. 2325-33; Bollag, D.M., *Epothilones: novel microtubule-stabilizing agents*. Expert Opin. Invest. Drugs, 1997. **6**(7): p. 867-873. As a result, Epothilone B **1**, and Epothilone A, **2**, were both isolated from the myxobacterium *Sorangium cellulosium* and the two dimensional structures were determined by the Merck group using NMR spectroscopic methods (HMBC), and the X-ray structure was published by the GBF group. Höefle, G., *et al.*, *Antibiotics from gliding bacteria. 77. Epothilone A and B - novel 16-membered macrolides with cytotoxic activity: isolation, crystal structure, and conformation in solution*. Chem. **1996**, **108**, 1671-1673; Angew. Chem., Int. Ed. Engl., 1996. **35**(13/14): p. 1567-1569. Both macrolides **1** and **2** appear to possess identical modes of action to Taxol, but are thousand-fold more potent in multidrug resistant cell lines.



Epothilone B, 1, R = Me
Epothilone A, 2, R = H



Taxol, 3

Taxol 3 is perhaps one of the most structurally complex anticancer agents known. Since its discovery in the early 1970's, it has received great attention from the scientific and medical community. Borman, S., *Scientists Mobilize To Increase Supply of Anticancer Drug Taxol*, in *Chem. & Engr. News*. 1991. p. 11-18. Taxol binds to the microtubule, or polymeric, form of tubulin with micromolar K_D values and stabilizes the microtubule pool by blocking the transition between G2 and M phases of cell growth. Taxol has a specific binding site in the polymeric tubulin. While other agents which arrest mitosis are known and are in clinical use for cancer chemotherapy, Taxol has elicited much attention for its efficacy against drug-refractory tumors, most notably ovarian but also metastatic breast, head and neck, melanoma and lung cancers. Taxol has recently been approved by the Food and Drug Administration for treatment of ovarian cancer (1992), breast cancer (1994) and is expected to be approved for other cancers. Riondel, J., *et al.*, *Cancer Chemother. Pharmacol.*, 1986. **17**: p. 137. Thus, while Taxol finds clinical promise against refractory cancers, substantial problems are none the less associated with this anticancer agent. Taxol is only poorly water soluble necessitating its administration in Chremophor, a solvent that in itself can be more toxic than Taxol and has caused a number of clinical problems. Further, more serious complications include peripheral neuropathy, neutropenia, cardiac arrhythmias, and less problematical, alopecia. Perhaps not surprisingly, Taxol is itself a genetic toxin at levels comparable to those in clinical use. Finally, perhaps some of the toxicity issues are related to the short plasma half-life of Taxol (less than 5 hrs). Kumar, G., T. Walle, and U. Walle, *Cytochrome P450 3A-Mediated Human Liver Microsomal Taxol 6a-Hydroxylation*. *J. Pharmacol. Exp. Ther.*, 1994. **268**: p. 1160-1165.

The most interesting feature of Epothilone B is that it behaves essentially identically to Taxol 3 *in vitro*, yet is thousand-fold more active than Taxol in cancerous

cells which have acquired multiple drug resistance (MDR), has the advantage of better solubility than taxol, and can be obtained in multigram quantities. Bollag, D.M., *et al.*, *Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action*. Cancer Res., 1995. **55**(11): p. 2325-33; Bollag, D.M., *Epothilones: novel microtubule-stabilizing agents*. Expert Opin. Invest. Drugs, 1997. **6**(7): p. 867-873; Buck, S.B., *et al.*, *Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action*. Chemtracts, 1998. **11**(9): p. 671-677; Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Seminars in Oncology* **1992**, *19*, 622-638. In P-glycoprotein (the MDR protein which pumps drugs out of the cell) expressing KBV-1 cells, for example, IC₅₀ values for Taxol are **2.3 X 10⁻⁵ M** but are **5.8 X 10⁻⁸ M** for **Epothilone B**. These effects seem to be expressed on a mechanistic level; Epothilone B binds competitively with Taxol to the Taxol binding site but is presumably a much poorer P-glycoprotein substrate. Since the most remarkable feature of Taxol is its good activity against MDR cancers, and Epothilone B is far superior to Taxol in this regard, it is likely that Epothilone B will evolve to have a much greater therapeutic index than Taxol against MDR cancers. At the very least, Epothilone B (analogs) would be a useful next line of clinical chemotherapy once Taxol resistance had been encountered. While much more research remains to be done for the epothilones, it still seems as if Epothilone B could well become an anticancer drug that is clinically far superior to Taxol.

Epothilone B has one main ring, a 16-membered lactone ring with a total of 7 stereocenters. In comparison, Taxol has four main rings and 11 stereocenters and has occupied the best minds in synthetic organic chemistry for at least the last ten years with no less than 30 groups working on its total synthesis at one time or the other over this period of time. While its total synthesis was completed by Holton, Danishevsky and Nicolaou (Holton, R.A., *et al.*, *First Total Synthesis of Taxol. 1. Functionalization of the B Ring*. J. Amer. Chem. Soc., 1994. **116**: p. 1597-1598), the incredible complexity of Taxol has hampered the development of a viable total synthetic route by which Taxol or its analogs could be obtained for clinical use. However, the supply issue for Taxol was solved to some extent by partial synthesis from baccatins, available from ornamental yew plants. Ojima, I., *et al.*, *New and Efficient Approaches to the Semisynthesis of Taxol and Its C-13 Side Chain Analogs by Means of β -Lactam Synthons Method*. Tetrahedron, 1992. **48**: p. 6985-7012.

The synthesis of Epothilone B, on the other hand, should not represent an insurmountable task. Epothilone B has yet to receive the attention that Taxol has, but is in principle inexhaustibly available from fermentation. However, practical experience has led the Merck group to abandon the preparation of Epothilones by fermentation due to extremely poor yields, a finding confirmed by NaPro Biotherapeutics. Thus, in order to obtain Epothilone B for clinical trials, semi-synthetic modification, structure-activity relationship studies, and to make it commercially available, an efficient total synthesis is required.

Several excellent syntheses of Epothilone A and B have appeared in the last few years, as reported in Appendino, G. and G. Casiraghi, *The synthesis of epothilones: highlights from a year's race*. Chemtracts, 1998. **11**(9): p. 678-696. Numerous reported syntheses and partial syntheses, as well as patent-related publications have also appeared in the past few years in regards to Epothilone syntheses: Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem.* **1998**, *110*, 2121-2153; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2014-2045; Mulzer, J. *Chem. Mon.* **2000**, *131*, 205-238; Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 100073-10092; Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschinger, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960-7973; Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974-7991; Schinzer, D.; Limberg, A.; Bauer, A.; Boehm, O. M.; Cordes, M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523-524; May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597-1598; White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407-5413; Martin, H. J.; Drescher, M.; Mulzer, J. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 581-583; Sawada, D.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 209-213; Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456-7467; Panicker, B.; Karle, J. M.; Avery, M. A. *Tetrahedron*, **2000**, *56*, 7859-7868 and references therein;

Vite, G.D., *et al.*, *syntheses of epothilone derivatives and intermediates for use in treatment of hyperproliferative cellular disease*, 1999: PCT Int. Appl.;

Vite, G.D., *et al.*, *Epothilone derivatives*, 1999: PCT Int. Appl.;

Klar, U., et al., *New method for the preparation of the C(1)-C(6)-segment of epothilone and epothilone derivatives*, 1999: Ger. Offen.;

Klar, U., et al., *New (C13-C15)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives*, 1999: Ger. Offen.;

Klar, U., et al., *New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives*, 1999: Ger. Offen.;

Klar, U., et al., *Preparation of new epothilone derivatives as pharmaceutical agents*, 1999: PCT Int. Appl.;

Kim, S.H. and R.M. Borzilleri, *A process for the preparation of ring-opened epothilone intermediates which are useful for the preparation of epothilone analogs*, . 1999: PCT Int. Appl.;

Kim, S.H. and J.A. Johnson, *A process for the reduction of oxiranyl epothilones to olefinic epothilones*, 1999: PCT Int. Appl.;

Wessjohann, L.A. and T. Gabriel, *Preparation of epothilone synthon*, 1998: Ger. Offen.;

Bosslet, K., et al., *Glycoconjugates of antitumor drugs with improved in vivo compatibility*, 1998: Ger. Offen.;

Methods for preparation of epothilone derivatives, 1998: Ger. Offen.;

Schinzer, D., et al., *Method for producing epothilones and the intermediate products obtained during the production process*, 1998: PCT Int. Appl.;

Schinzer, D., A. Limberg, and O.M. Boehm, *Intermediate products within the total synthesis of Epothilones A and B*, 1997: Ger.;

Danishefsky, S.J., et al., *Synthesis of epothilones, intermediates and analogs for use in treatment of cancers with multidrug-resistant phenotype*, 1999: PCT Int. Appl.;

Rosen, N., *et al.*, *A method of treating cancer using an antineoplastic agent-prenyl-protein transferase inhibitor combination, and compound preparation*, 1998: PCT Int. Appl.;

Hunter, W.L., *Antimicrotubule compositions and methods for treating or preventing inflammatory diseases*, 1998: PCT Int. Appl.;

Höfle, G. and M. Sefkow, *Procedure for the preparation of epothilones with a modified side chain*, 1998: PCT Int. Appl.;

Danishefsky, S.J., *et al.*, *Synthesis of epothilones, intermediates thereto, analogs and uses thereof*, 1999: PCT Int. Appl.;

Reichenbach, H., *et al.*, *Epothilone C, D, E and F, production process, and their use as cytostatics well as phytosanitary agents*, 1998: PCT Int. Appl.;

Höfle, G. and M. Kiffe, *Preparation of epothilone derivatives as agrochemicals and pharmaceuticals*, 1997: PCT Int. Appl.;

Höfle, G., *et al.*, 1993: (GBF), DE;

Nicolaou, C.K., *et al.*, *Preparation of epothilone analogs as anticancer agents*, 1998: PCT Int. Appl.;

Hofle, G. and M. Sefkow, *Procedure for the preparation of epothilones with a modified side chain*, 1998: PCT Int. Appl.;

Hofle, G. and M. Kiffe, *Preparation of epothilone derivatives as agrochemicals and pharmaceuticals*, 1997: PCT Int. Appl.;

Hoefle, G. and M. Kiffe, *Preparation of epothilone derivatives as agrochemicals and pharmaceuticals*, 1997: Ger. Offen.;

Hoefle, G., *et al.*, *Epothilone derivatives*, 1993: Ger. Offen.;

Mulzer, J. and A. Mantoulidis, *Method for the production and use of thiazole derivatives*, 1999: PCT Int. Appl.;

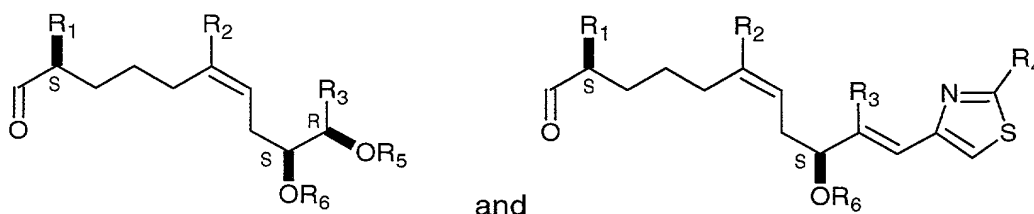
Mulzer, J. and A. Mantoulidis, *Method for the preparation and assembly of intermediate products in the production of epothilones*, 1998: Ger. Offen.; and

May, S.A., *Total synthesis of complex natural products: i. endiandric acid a. ii. (+/-)-adrenosterone. iii. (-)-epothilone b*, . 1998. p. 172.

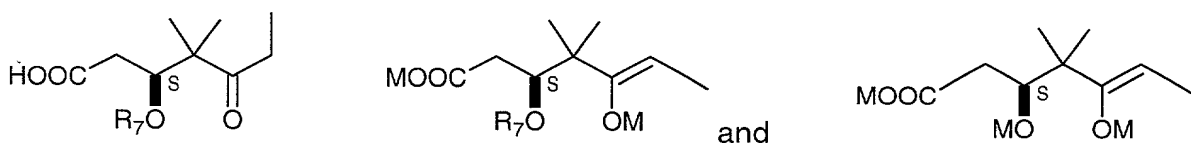
However, there still remains a need for approaches that will provide an efficient route to Epothilone A, B or Deoxyepothilone A or B, or to analogs and derivatives of these compounds.

Summary of the Invention

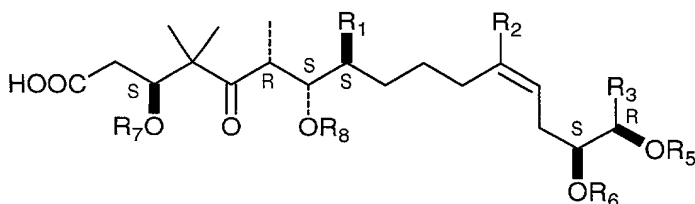
According to the present invention then, a new and useful method is provided for use in producing epothilones and analogs and derivatives thereof. The method comprises performing an aldol condensation of a first compound selected from the formulas:



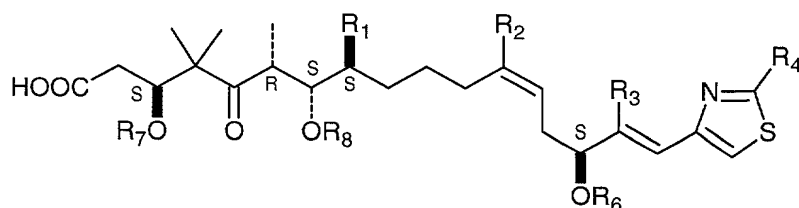
and stereoisomers thereof, with a second compound selected from the formulas:



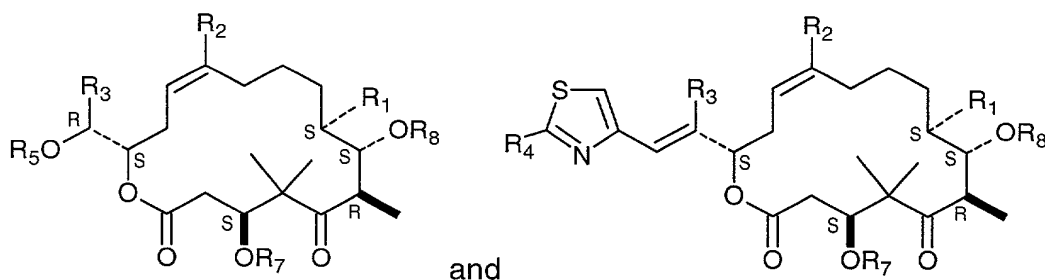
and stereoisomers thereof, thereby to form a third compound selected from the formulas:



and

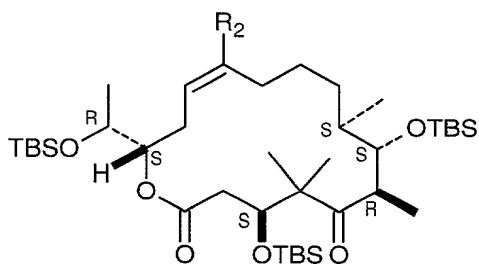


and stereoisomers thereof, wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; wherein R_5 , R_6 , R_7 and R_8 are each selected from H and a protecting group; and wherein M is an alkali metal; and performing a macrolactonization of the third compound thereby to form a fourth compound selected from the formulas:

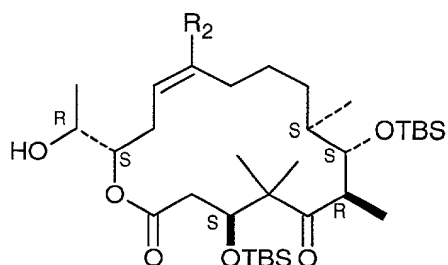


and stereoisomers thereof, wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; and wherein R_5 , R_7 and R_8 are each selected from H and a protecting group. R_1 , R_3 and R_4 may each be methyl when R_2 is H or methyl, and at least one of R_5 - R_8 may be TBS. More broadly, R_5 may be selected from PMB, DPS and TBS; R_6 may be selected from H, TBS, TMS, TIPS, PMBM and SEM; R_7 may be selected from H, TBS, TROC, and $-CO(CH_2)_4CH_3$; and R_8 may be selected from H and TBS.

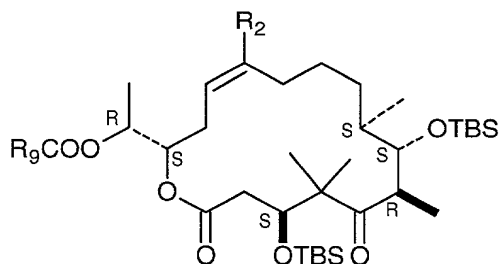
The fourth compound may be of a formula selected from:



and stereoisomers thereof, where R_2 is H or methyl; and the fourth compound may be converted to a fifth compound of a formula selected from:

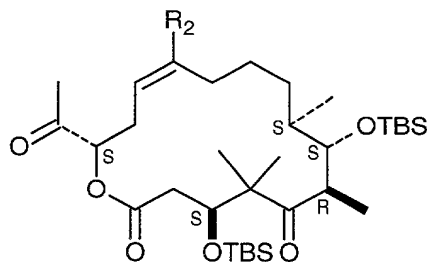


and stereoisomers thereof, where R_2 is H or methyl. The fifth compound may be converted to a sixth compound of a formula selected from:

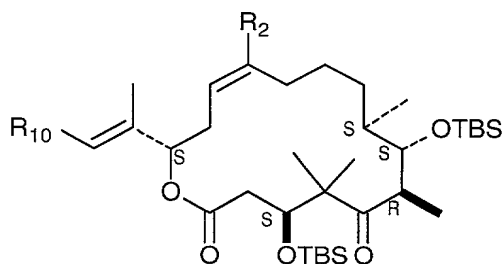


and stereoisomers thereof, where R_2 is H or methyl and wherein R_9 is selected from alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo.

The fifth compound may alternatively be converted to a sixth compound of a formula selected from:

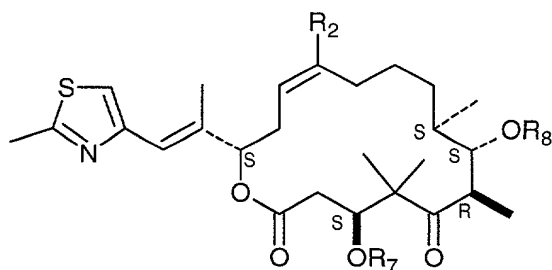


and stereoisomers thereof, where R_2 is H or methyl, and the fifth compound may be converted to a sixth compound of a formula selected from:



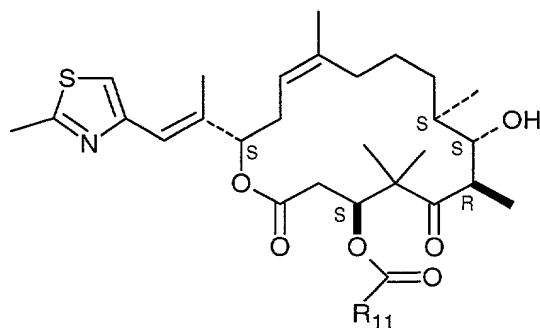
and stereoisomers thereof, where R_2 is H or methyl and wherein R_{10} is selected from alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo.

The fourth compound may be of a formula selected from:

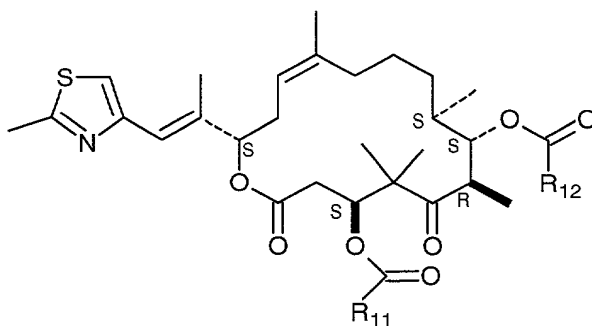


and stereoisomers thereof, where R_2 is H or methyl, R_7 is H or TBS, and R_8 is H, TBS, or TROC, and the fourth compound may be further converted to Epothilone B.

When R_7 and R_8 each are H, the fourth compound may be further converted to a fifth compound of a formula selected from:

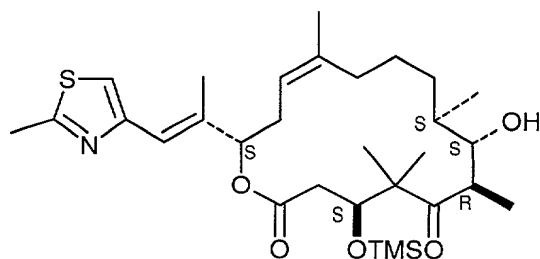


and stereoisomers thereof, wherein R_{11} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof; and the fifth compound may be further converted to a sixth compound of a formula selected from:

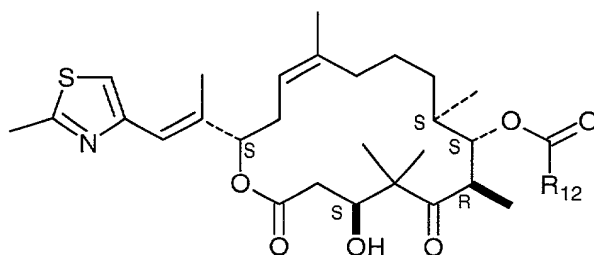


and stereoisomers thereof, wherein R_{11} and R_{12} are each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof.

Alternatively, the fourth compound may be further converted to a fifth compound of a formula selected from:

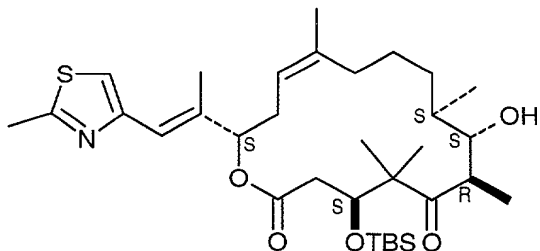


and stereoisomers thereof, and the fifth compound may be further converted to a sixth compound of a formula selected from:

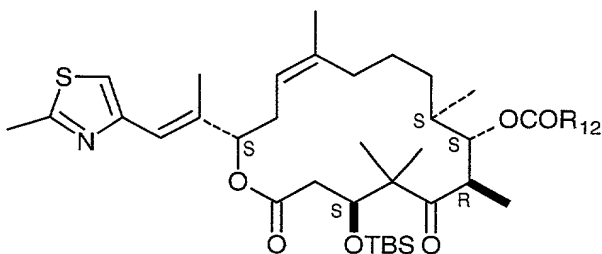


and stereoisomers thereof, wherein R_{12} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof.

When R_7 is TBS and R_8 is TROC, the fourth compound may be further converted to a fifth compound of a formula selected from:

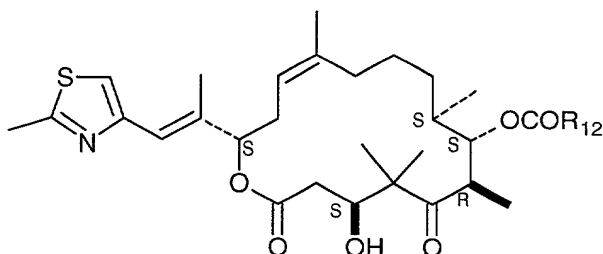


and stereoisomers thereof, and the fifth compound may be further converted to a sixth compound of a formula selected from:

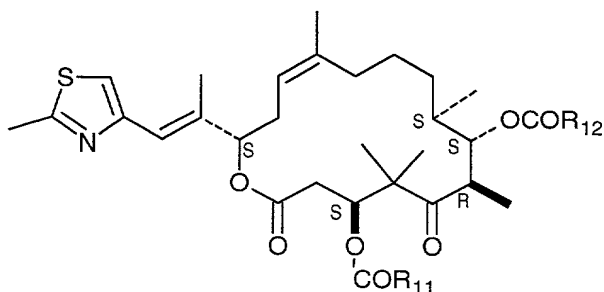


and stereoisomers thereof, wherein R_{12} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions

thereof. The sixth compound may be further converted to a seventh compound of a formula selected from:

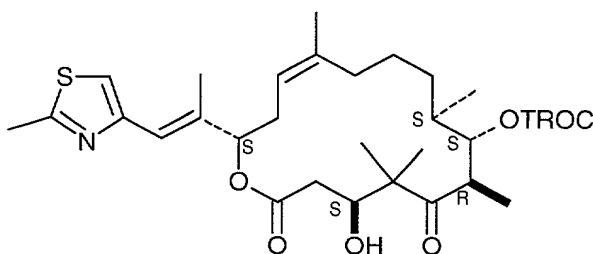


and stereoisomers thereof, wherein R_{12} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof, and the seventh compound may be further converted to an eighth compound of a formula selected from:

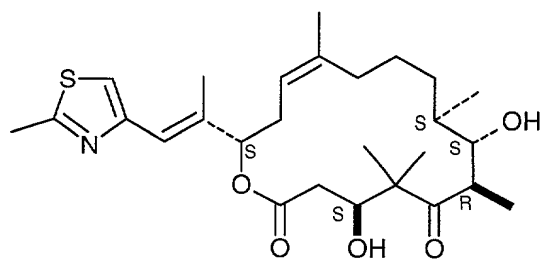


and stereoisomers thereof, wherein R_{11} and R_{12} are each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof.

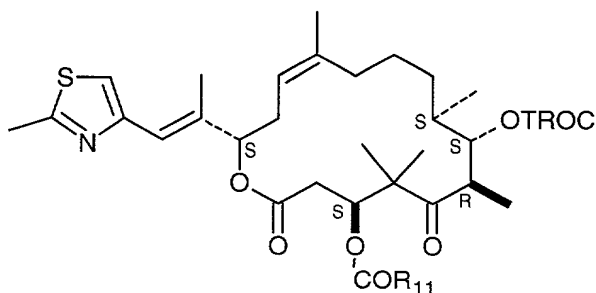
Alternatively, the fourth compound may be further converted to a fifth compound of a formula selected from:



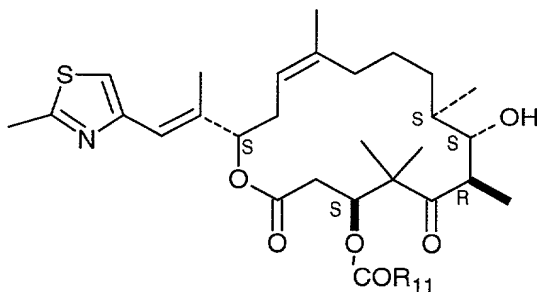
and stereoisomers thereof, and the fifth compound may be further converted to a sixth compound of a formula selected from:



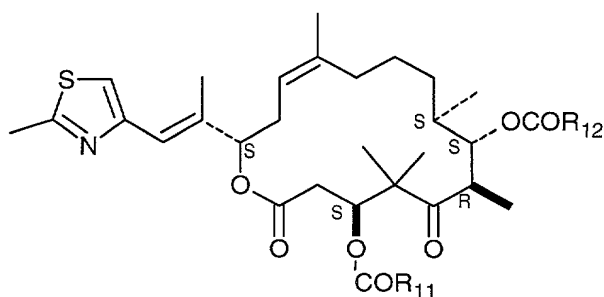
and stereoisomers thereof. The sixth compound may be further converted to Epothilone B. As a further alternative, the fifth compound may be further converted to a sixth compound of a formula selected from:



and stereoisomers thereof, wherein R_{11} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof, and the sixth compound may be further converted to a seventh compound of a formula selected from:

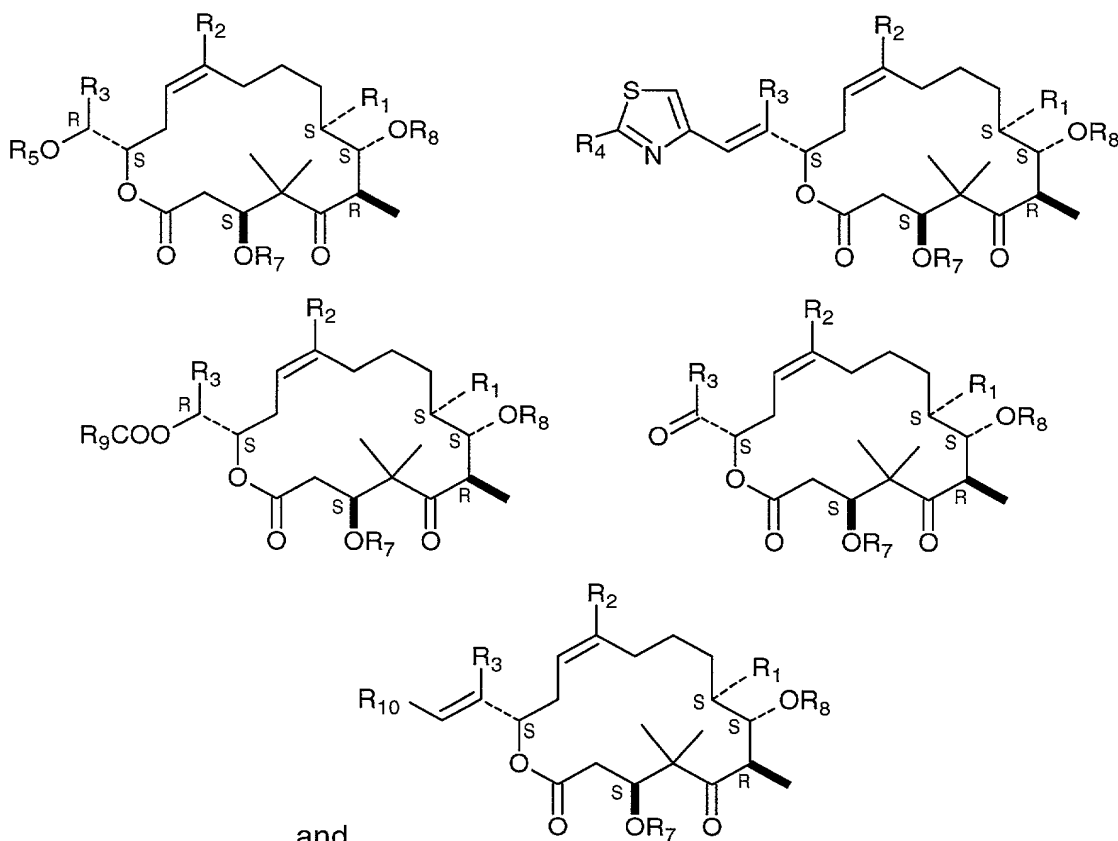


and stereoisomers thereof, wherein R_{11} is selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof. This seventh compound may be further converted to an eighth compound of a formula selected from:



and stereoisomers thereof, wherein R_{11} and R_{12} are each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof.

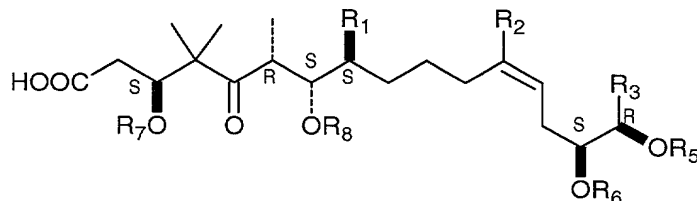
The present invention also relates to chemical compounds, which may be formed according to the above method or by other methods, and in particular to compounds of the formulas:



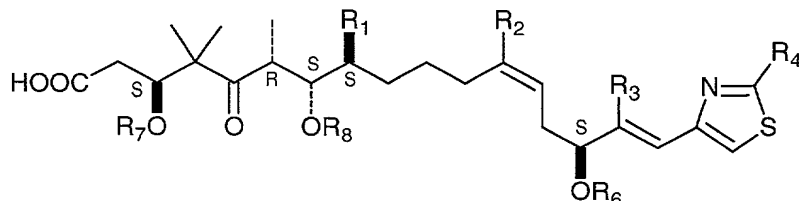
and stereoisomers thereof, wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; wherein R_5 and R_6 are each selected from H and a protecting group; wherein R_7 is selected from H, a protecting group and COR_{11} ; wherein R_8 is selected from H, a

protecting group and COR₁₂; wherein R₉ is selected from alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; wherein R₁₀ is selected from alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; and wherein R₁₁ and R₁₂ are each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof.

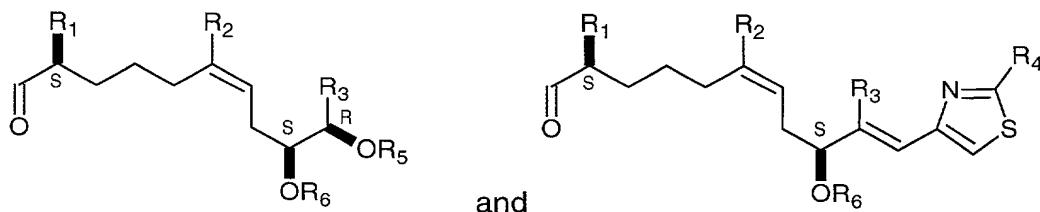
The present invention also relates to chemical compounds having a formula selected from:



and

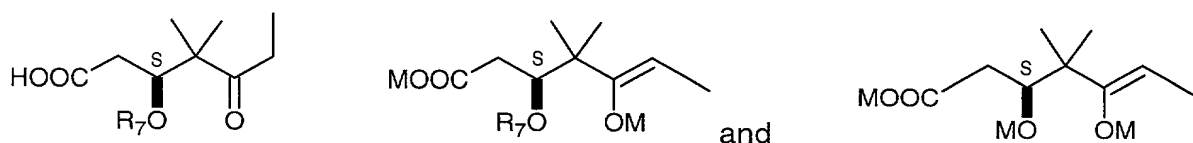


and stereoisomers thereof, wherein R₁, R₂, R₃ and R₄ are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; and wherein R₅, R₆, R₇ and R₈ are each selected from H and a protecting group, as well as a method for producing such chemical compounds that are useful in producing epothilones and analogs and derivatives thereof. Broadly, the method comprises performing an aldol condensation of a first compound selected from the formulas:



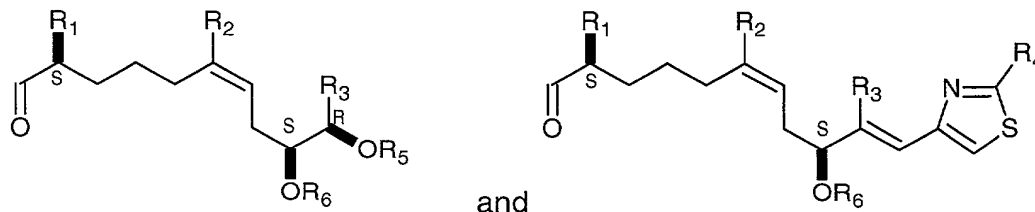
and

with a second compound selected from the formulas:



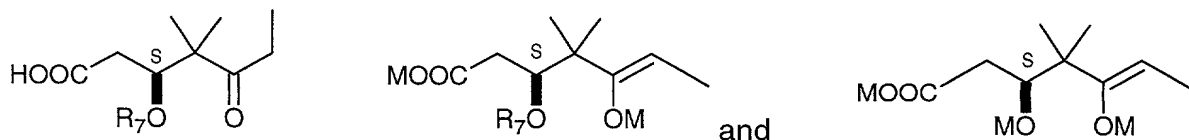
wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; wherein R_5 , R_6 , R_7 and R_8 are each selected from H and a protecting group; and wherein M is an alkali metal.

The present invention is also directed to chemical compounds having a formula selected from:



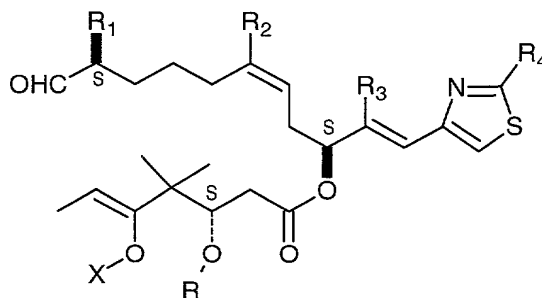
and stereoisomers thereof, wherein R_1 , R_2 , R_3 and R_4 are each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted aryl, cycloalkyl and heterocyclo; and wherein R_5 and R_6 are each selected from H and a protecting group, as well as a number of methods for producing such chemical compounds useful in producing epothilones and analogs and derivatives thereof.

The present invention is further directed to chemical compounds having a formula selected from:

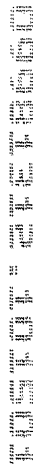


wherein M is an alkali metal, such as lithium, and wherein R_7 is selected from H and a protecting group, as well as processes for producing such chemical compounds useful in producing epothilones and analogs and derivatives thereof.

Additionally, the present invention relates to a process for use in producing epothilones and analogs and derivatives thereof, comprising converting a first compound of a formula selected from:



and stereoisomers thereof to a second compound of a formula selected from:



These and other objects of the present invention will become more readily appreciated and understood from a consideration of the following detailed description of the exemplary embodiments of the present invention when taken together with the accompanying drawings, in which:

Figure 1 is a diagram of chemical reaction Scheme I according to the present invention;

Figure 3 is a diagram of chemical reaction Scheme II according to the present invention;

Figure 4 is a diagram of chemical reaction Scheme IV according to the present invention;

Figure 5 is a diagram of chemical reaction Scheme V according to the present invention;

Figure 5a is a diagram of chemical reaction Scheme Va according to the present invention;

Figure 6 is a diagram of chemical reaction Scheme VI according to the present invention;

Figure 7 is a diagram of chemical reaction Scheme VII according to the present invention;

Figure 8 is a diagram of chemical reaction Scheme VIII according to the present invention;

Figure 9 is a diagram of chemical reaction Scheme IX according to the present invention;

Figure 10 is a diagram of chemical reaction Scheme X according to the present invention;

Figure 11 is a diagram of chemical reaction Scheme XI according to the present invention;

Figure 12 is a diagram of chemical reaction Scheme XII according to the present invention;

Figure 13 is a diagram of chemical reaction Scheme XIII according to the present invention;

Figure 14 is a diagram of chemical reaction Scheme XIV according to the present invention;

Figure 15 is a diagram of chemical reaction Scheme XV according to the present invention;

Figure 16 is a diagram of chemical reaction Scheme XVI according to the present invention;

Figure 17 is a diagram of chemical reaction Scheme XVII according to the present invention;

Figure 18 is a diagram of chemical reaction Scheme XVIII according to the present invention;

Figure 19 is a diagram of chemical reaction Scheme XIX according to the present invention;

Figure 20 is a diagram of chemical reaction Scheme XX according to the present invention;

Figure 21 is a diagram of chemical reaction Scheme XXI according to the present invention;

Figure 22 is a diagram of chemical reaction Scheme XXII according to the present invention;

Figure 23 is a diagram of chemical reaction Scheme XXIII according to the present invention;

Figure 24 is a diagram of chemical reaction Scheme XXIV according to the present invention;

Figure 25 is a diagram of chemical reaction Scheme XXV according to the present invention;

Figure 26a is a diagram of chemical reaction Scheme XXVIa according to the present invention;

Figure 26b is a diagram of chemical reaction Scheme XXVIb according to the present invention;

Figure 27 is a diagram of chemical reaction Scheme XXVII according to the present invention;

Figure 28 is a diagram of chemical reaction Scheme XXVIII according to the present invention;

Figure 29 is a diagram of chemical reaction Scheme XXIX according to the present invention;

Figure 30 is a diagram of chemical reaction Scheme XXX according to the present invention;

Figure 31 is a diagram of chemical reaction Scheme XXXI according to the present invention;

Figure 32 is a diagram of chemical reaction Scheme XXXII according to the present invention;

Figure 33 is a diagram of chemical reaction Scheme XXXIII according to the present invention;

Figure 34 is a diagram of chemical reaction Scheme XXXIV according to the present invention;

Figure 35 is a diagram of chemical reaction Scheme XXXV according to the present invention;

Figure 36 is a diagram of chemical reaction Scheme XXXVI according to the present invention; and

Figure 37 is a diagram of chemical reaction Scheme XXXVII according to the present invention.

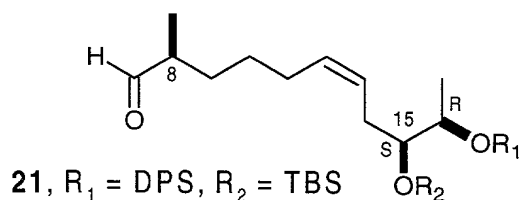
Detailed Description of the Invention

Total Synthesis of Epothilone A

Epothilones B, **1** and A, **2** (shown above) contain a 16 membered lactone ring with hydroxyl groups at C-3 and C-7, ketone at C-5, epoxide at C-12,13 and an aryl containing side chain at C-16. Both lactone and ketone groups contain β -hydroxy functionality which can presumably be installed via asymmetric aldol condensation. Overall, Epothilone is a typical macrolide possessing an array of alternating methyl and hydroxyl groups of varying stereochemistries.

We have envisioned the deconstruction of **1** and **2** retrosynthetically as shown in Figure 1 (Scheme I). The underlying key construction step in our approach employs a copper (I) promoted Normant coupling of the monoterpene-derived Grignard of **6**, with propyne followed by trapping of the resulting organocopper intermediate with Sharpless epoxide **5**. This procedure allows for a rapid preparation of the aldehyde **7** required for Aldol condensation with the known keto-acid **10**, furnishing the acyclic acid **11**. Macrolactonization to **12** followed by simple functional group manipulations is expected to provide Epothilone B.

A second retrosynthetic scheme we developed was based on the production of Epothilone A **2** by alkyne opening of an epoxide, which later lead stereoselectively to a cis-olefin and thereby the 12,13-cis epoxide moiety as shown in Figure 2 (Scheme II). A few aspects of this work have been published (Bijoy, P. and M.A. Avery, *Synthetic studies directed towards epothilone A: enantioselective synthesis of a C7-C15 carboxaldehyde segment*. Tetrahedron Lett., 1998. **39**(3/4): p. 209-212), and application to the total synthesis of Epothilone A, **2**, has been pursued in parallel to the alternate route outlined in Figure 1 (Scheme I). Apart from the aldehyde **21**:



reported in our earlier work we also prepared the aldehydes **20a** and **20b** essentially having different protecting groups at the secondary hydroxyl groups, as shown in Figure 3 (Scheme III).

The synthesis of **20a** and **20b** shown in Figure 3 (Scheme III) involves preparation of the alkynylalane **14** from the alkyne **13**, that upon opening of **5** and dil.HCl quench gave the diol **15**. Selective reduction of the alkyne **15** (Lindlar reduction) provided the required *Z*-olefin **16**. A sequence of events transforms **16** into iodide **17**: selective tosylation at the primary alcohol; protection of the secondary alcohol as the TBS (*tert*-butyldimethylsilyl) occurs without disturbing the primary tosylate, and finally, NaI displaces the tosylate to give the iodide **17**. Alkylation of this iodide with the enolate of propionyl amide **18** prepared from the (-)-camphorsultam afforded the homologated material, auxiliary intact, **19**. DIBAH reduction of the adduct **19** resulted in the aldehydes **20a** and **20b**. The aldehydes **20a** and **20b** are the desmethyl counterparts to aldehyde **7** in Figure 1 (Scheme I). The overall process is 7 steps from pentynyl derivative **13**.

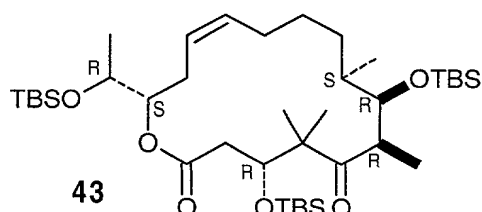
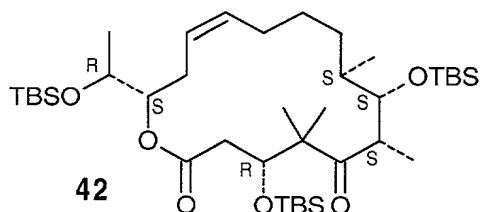
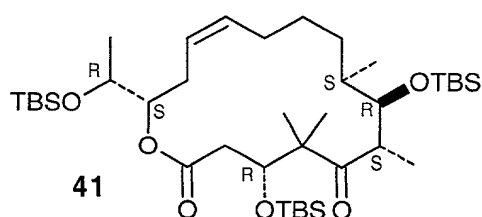
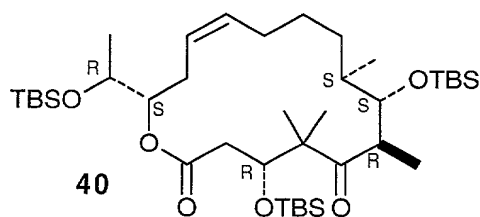
Alternatively, the side-chain thiazole ring could be installed to provide the aldehyde **29** as outlined in Figure 4 (Scheme IV). In this approach treatment of **16a** with MEM-Cl yielded the bis-MEM ether. Desilylation of the bis-MEM ether with fluoride ion gave **22**, oxidation of which then provided the ketone **23**. Horner Emmons Reaction of **23** with the phosphonate anion of **24** then afforded the diene **25**. Remarkably, **25** could not be deprotected readily under expected conditions, but required concentrated HCl solution to effect transformation into the diol **26**. The primary alcohol of diol **26** was smoothly tosylated, and the secondary alcohol silylated with TBSOTf. Upon Sn₂ displacement of the primary tosylate, the iodide **27** was isolated as a light yellow, reasonably stable oil. Alkylation of the iodide with the anion of sultam **18** gave adduct **28**. Reduction to the adduct **28** with DIBAH provided the requisite aldehyde **29** which was identical in all respects compared to the one reported by Nicolaou (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy*. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991).

For aldol condensation required by Scheme I, the silyl-protected keto-acid **10** was required. As reported by a unique route, Nicolaou (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy*. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991) reported that the silyl-protected keto-acid **10** had a rotation ($[\alpha]_D$) of +16.1°. According to De Brabander (De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of*

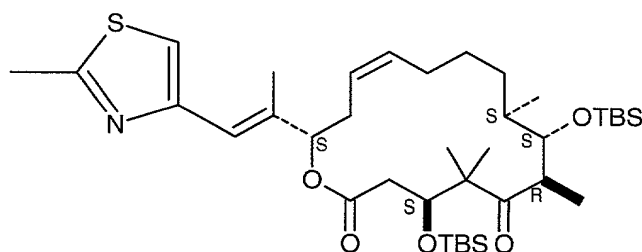
the C(1)-C(6) and C(7)-C(12) fragments. Synlett, 1997(7): p. 824-826), this acid could be prepared from the N-propionate of the (+)-Sultam **30** as outlined in Figure 5 (Scheme V). De Brabander reported a rotation value for sultam **33** of +119°, depicted the alcohol stereocenter as *S*, and deposited the crystal structure in the Cambridge Crystallographic Database (CCD). However, perusal of structure **33** in the CCD shows clearly that the alcohol stereocenter is *R*, opposite of that drawn in the paper.

Furthermore, no rotation value was given for the acid **34** except stating that this acid was previously reported by Nicolaou. Without confirming the X-ray results reported by De Brabander by logging into the CCD, one would assume the correct acid to be derived from Scheme V. In fact, when we prepared the TBS-acid **34** as outlined, the rotation value we obtained was in good agreement with Nicolaou at +17.4°. DeBrabander later corrected his first publication. De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of the C(1)-C(6) and C(7)-C(12) fragments. [Erratum to document cited in CA127:234203]*. Synlett, 1998(6): p. 692; De Brabander, J., S. Rosset, and G. Bernardinelli, *Towards a synthesis of epothilone A. Rapid assembly of the C1-C6 and C7-C12 fragments. [Erratum to document cited in CA127:234203]*. Synlett, 1998(3): p. 328.

When the TBS acid we assumed was **10** (shown in Figure 5 (Scheme V)) was condensed with aldehyde **21**, reduced product **35** was obtained as shown in Figure 5a (Scheme Va). In the course of investigations, it was determined that the bulky diphenyltertbutylsilyl (DPS) & tertbutyldimethylsilyl (TBS) groups were responsible for this unexpected result. When the aldehyde **20b** (TMS replaces TBS) was used, the aldol reaction did take place but the yields were only moderate. On the other hand the aldol reaction with **20a** went much more smoothly to give a mixture of 4 diastereomeric aldol adducts in good yields. In order to convert these linear products to materials we could match to literature, we trapped the intermediate aldolates with TBSOTf, and the labile TMS group was then lost during chromatography to give **36-39** as shown in Figure 6 (Scheme VI). The isomers as a mixture were cyclized with Cl₃C₆H₂COCl, pyridine, DMAP to afford lactones **40-43**:



As indicated in Figure 7 (Scheme VII) and Figure 8 (Scheme VIII), each diastereomer was then selectively deprotected, oxidized to methyl ketone (evident by NMR), and finally, reacted with Horner-Emmons reagent **24** to furnish penultimate intermediates on the way to a route to Epothilone A reported by Nicolaou. In this report, spectral data for **46**:



was slightly different from each isomer brought forward, intermediates **45,47-49** shown in Figure 7 (Scheme VII) and Figure 8 (Scheme VIII). None of these products matched known material. Each stereocenter was individually checked, including the synthesis of the α -methyl diastereomer of the aldehyde **29** to make sure we have the correct stereochemistry. Finally, we checked the lactones from Daneshevsky's synthesis of epi-epothilones, and matched lactone **45** with known material. This clearly indicated that the keto-acid reported to be **10** was incorrectly assigned by De Brabander and was in fact keto-acid **34**. This also confirms the error in reporting the sign of the optical rotation of **10** by Nicolaou.

With this revelation at hand, we prepared **10** with the opposite sign of rotation as reported by Nicolaou, as shown in Figure 9 (Scheme IX), by condensation with the N-

acetyl derivative **51**, prepared from (-)-sultam (**50**) and acetyl chloride, with aldehyde **9**. After silylation and removal of auxillary, we obtained **10** with sign of rotation opposite that reported by Nicolaou (Scheme IX).

As final proof of this reassignment to the sultam route to **10**, we condensed bonafide **10** with aldehyde **29** as shown in Figure 10 (Scheme X). The resulting acids **53** and **54** were identical to reported materials by proton and carbon NMR, and the signs of rotation were as reported. Finally, selective deprotection of **54** to give the alcohol **55** was followed by cyclization to afford the reported precursor to Epothilone A, **46**. This formally completes the synthesis of Epothilone A.

In order to reduce the total number of steps en route to the epothilones, the trianion of acid **56** has been examined in a model system such as benzaldehyde and gave outstanding chemical yields, but in a 1:1 ratio of syn,syn to syn,anti. With **21** however, **56** led to sole production of the reduced aldehyde, alcohol **35**, as shown in Figure 11 (Scheme XI). On the other hand reaction with **29** resulted in the aldol products **57** and **58**. Removal of the TBS group of **58** using TBAF afforded the triol acid **59**, which on macrocyclization gave **60**, the precursor to Epothilone A (Scheme XI).

Presumably, macrolactonization of the triol-acid **59** gave the desired product based on the relative rates of 4- vs 8- vs 16-membered ring closures, as indicated in Figure 12 (Scheme XII). The relative rates are 0.58, 1.5×10^{-4} , and 3×10^{-3} , respectively, clearly indicating an initial preference for β -lactone formation. Casadei, M.A., C. Galli, and L. Mandolini, *Ring-Closure Reactions. 22. Kinetics of Cyclization of Diethyl(w-Bromoalkyl)malonates in the Range of 4- to 21- Membered Rings. Role of Ring Strain*. J. Amer. Chem. Soc., 1984. **106**: p. 1051-1056. However, it is also known that β -lactones are excellent active esters and react with alcohols to give ring-opened esters. Lactonization conditions applied to **59** probably formed the β -lactone **61**, but subsequent *in situ* trans-lactonization resulted in formation of the desired 16-membered lactone **60**.

Similarly, reaction of **10** with the aldehyde **20a** resulted in the aldol adducts **62-65** which on further transformations as outlined previously afforded the corresponding cyclic lactones **46**, **70-72**, as shown in Figure 13 (Scheme XIII).

With reference to Figure 14 (Scheme XIV), in all of the above cases (e.g. Schemes VII, VIII, XII, etc.), the corresponding 3S alcohols **73** and ketones **44** provide

starting materials which can be derivatized and the resulting products **75** and **78** used as bioactive substances (R = alkyl, aryl, heterocyclic). Obviously, related 3R intermediates **74** and **77** can be processed similarly to furnish the 3R products **76** and **79**. Diastereomeric materials can be carried forward in the same fashion.

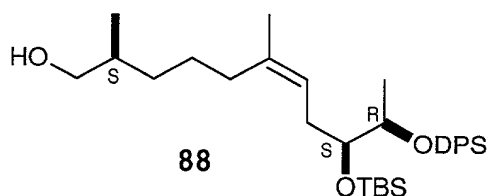
Total Synthesis of Epothilone B

Total synthesis of **1** via Scheme I is based upon a Normant reaction in which an acetylene derivative such as propyne or TMS-acetylene was coupled to a Grignard reagent in the presence of Cu(I), and the intermediate cuprate was then used as a nucleophile to open a Sharpless epoxide such as **5**. Numerous cases were examined to find the best conditions and protecting groups to facilitate the overall synthesis, and started with the addition of the TIPS protected Grignard **80** to propyne as outlined in Figure 15 (Scheme XV). Addition of Cu(I) to the Grignard derived from **80**, followed by propyne resulted in an intermediate vinyl cuprate **80a** that could not effect opening of epoxide **5b**, but could be quenched with iodine to furnish the Z-vinyl iodide **81** in excellent yield. Metallation of the vinyl iodide with alkyl lithium and metal exchange with an aluminum chloride provided a sufficiently reactive vinylalane which effected opening of the DPS protected epoxide **5b** to give the differentially protected triol **82**. Desilylation of **82** with dilute acid and selective tosylation gave the tosylate **84**, that upon silylation with TBSOTf gave disilylated tosylate **85**. Upon Sn2 displacement with iodide, the stable iodide **86** was formed and alkylated with the propionosultam **18** to give **87**, by analogy to formation of **20**. Overreduction with lithium aluminum hydride gave alcohol **88**, and finally, reoxidation with pyridine-SO₃ complex furnished the target aldehyde **21a**.

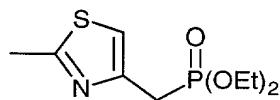
An alternative approach to the preparation of the aldehyde **21** which bypassed the iodoalkene intermediate **81** was examined involving addition of an olefinic Grignard derived from **89** at the outset instead of the TIPS ether **80**, as shown in Figure 16 (Scheme XVI). Apparently, the presence of a g-TIPSO moiety had a detrimental effect on the ensuing epoxide opening via cuprate intermediate **80a**. On the other hand, the cuprate intermediate **89a** suffered no such limitation after ligand exchange with pentynyl lithium, and smoothly effected opening of **5b** to furnish the alcohol-diene **90** in excellent yields. Conversion to the known tosylate **85** was then accomplished as follows: Silylation gave the TBS ether **91**; oxidation of the less hindered terminal olefin was

achieved with AD-mix α , and the resulting diol cleaved to aldehyde **92** with periodate. Finally, reduction to alcohol and tosylation gave **85**.

Unfortunately however, aldehyde **21a** behaved identically to **21** in attempted aldol condensation, giving reduction product **88**:



Therefore, as before, some adjustment had to be made to the protection scheme in order to achieve the aldol condensation. As shown in Figure 16 (Scheme XVI), use of **5a** instead of **5b** gave the expected opening product **91** that could be protected with a smaller silyl group, TMSOTf to furnish the bisprotected diene **93**. AD mix as before, and glycol cleavage gave aldehyde **95**, that could be reduced and tosylated to provide **96**. Following the reaction of Figure 17 (Scheme XVII) as before with DPS/TBS protection, now substituting TBS/TMS **96** allowed for the production of aldehyde **100**. With less hydrophobic steric bulk at the terminus of the side chain (e.g. DPS vs. TBS), the aldol condensation occurred more readily than was the case in the Epothilone A series, Figure 13 (Scheme XIII). Thus, upon treatment of **100** with **10**, aldol adducts could be obtained and silylated *in situ* as before, becoming immediately ready for cyclization after silica gel chromatography. As shown in Figure 18 (Scheme XVIII), from this mixture, **104** (or **11** from Scheme I) cyclized in the usual manner to furnish the precursor to Epothilone B, **105**. Selective desilylation as before, giving a free alcohol **106**, and oxidation gave the ketone **12**, and Horner-Emmons Reaction with **24**:



gave the bis-TBS ether of deoxyepothilone B, **107**. This is a known compound that has been converted to Epothilone B previously. Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy*. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991.

Clearly, as before in the Epothilone A series, Figure 14 (Scheme XIV), both alcohol **106** and ketone **12** serve as excellent precursors for the production of analogs as outlined in Figure 19 (Scheme XIX). Again, not only can the 3S series be

represented in this chemistry, but so can the 3*R* diastereomers. A variety of analogs of Epothilone B can be prepared in the side-chain such as esters **112/113** or styrenes or alkenes **110/111**.

Another alternative to the production of such differentially protected side-chain diols is shown in Figure 20 (Scheme XX). In this instance, the monoterpene *S*-dihydromyrcene **114** was employed for its chirality at the methyl position by ozonolytic treatment and reductive workup to furnish degraded alcohol **115**. Conversion to the bromide **116** was straightforward, and ensuing Normant reaction as before provided the extensively homologated diol-diene **117** or **118**, depending on whether epoxide **5a** or **5b** was used.

Protection in this case was with a TMS group when DPS was present from **5b**, alternatively, when the TBS epoxide was used resulting in **118**, then a paramethoxybenzyl (PMB) group was installed to provide **120**. Oxidation as before of either terminal alkene with ADmix followed by glycol cleavage with periodate gave the aldehydes **121** or **122**. Either of these aldehydes could be used in aldol condensation with acids such as **10** or **56** to provide cyclization precursors to either analogs or Epothilone B.

An additional and intriguing approach to the Epothilones involved the use of 4-methylpentyl bromide in the Normant reaction, shown in Figure 21 (Scheme XXI). In this case, the usual procedure gave **124** after water workup. However, the intermediate alkoxide could be capped with TMSOTf to furnish the bisprotected compound **125** directly. Alternatively, **124** could be blocked in a separate step with TMSOTf to arrive at the same compound **125**. Furthermore, as shown in Figure 22 (Scheme XXII), a PMB group could be placed on this position in a one pot procedure by adding PMB-Br to the cuprate intermediate, to access the PMB ether **129** directly. Diene **125** (Figure 21, Scheme XXI) was then hydroborated with bis(isopinocampheyl)borane to give, after oxidative workup with hydrogen peroxide, the *S*-methyl alcohol **126**. Cr(VI) workup (e.g. with PCC) gave the desired aldehyde **100** directly, or separate oxidation of the alcohol **126** afforded **100**. Conversions of **100** including its processing to natural product have been discussed (*vide supra*).

An alternative that incorporates the thiazole ring earlier in the synthesis is shown in Figure 22 (Scheme XXII). As discussed above, the PMB ether **129** can be formed in

a one pot procedure. It can be converted directly into the ketone **131**, a direct precursor for chiral hydroboration, or can be removed separately to give alcohol **130** which can be oxidized to the ketone **131**. In either event, the ketone **131** undergoes Horner-Emmons reaction to give the triene **132**. Now, in similar fashion to before, hydroboration with (lpc)₂BH can be followed up with either H₂O₂/NaOH to give alcohol **133**, or with Cr(VI) to give aldehyde **134** directly. The alcohol **133** can be oxidized separately to furnish aldehyde as a second route to **134**, a known compound whose spectral data was identical to ours. Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy*. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991.

The ensuing aldol condensation of **134** gave products identical to those reported, and subsequent conversions were uneventful. For the precedented reactions, dianion from **10** reacted with known **134** to give either the alcohol **135** (water workup) or the tri-TBS ether **137** (TBSOTf quench, or separate reaction). Either fully silylated acid **138** (literature) or fully desilylated acid **137** (novel) could be cyclized to furnish lactones **107** (literature) or **139** (literature). Their conversion to natural product is known, (Nicolaou, K.C., *et al.*, *Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy*. J. Am. Chem. Soc., 1997. **119**(34): p. 7974-7991) formally completing the total synthesis of Epothilone B.

A straightforward approach to Epothilone B involves the preparation of ketone **140** (e.g. from alcohol **128**), and effecting Horner-Emmons condensation with anion from **24** to furnish elaborated epoxide **141**, as shown in Figure 23 (Scheme XXIII). Normant reaction as before with bromide **123** and propyne, quenching the vinyl cuprate intermediate with **141**, and finally, trapping of the alkoxide final intermediate with TMSOTf, gave the triene **143**. Aldol condensation with the trianion **56a**, and simultaneous chromatography-deprotection provided the triol-acid **59**. Cyclization as before gives Deoxyepothilone B **60**, which could be epoxidized to afford the natural product **1**. Several points worthy of note, this Scheme represents essentially a seven step overall synthesis of Epothilone B. Furthermore, Deoxyepothilone B **60** may have superior properties to Epothilone B, thus shortening the route to 6 steps.

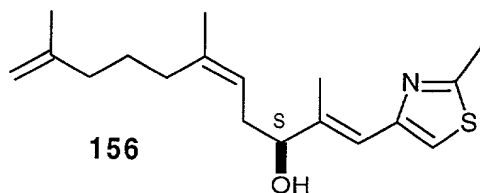
As shown in Figure 24 (Scheme XXIV), another related approach beginning with dihydro- α -myrcene **146** (Rienaecker, R., *.alpha.-Rhodinol and .alpha.-citronellol from optically active cis-pinane*. Chimia, 1973. **27**(2): p. 97-9), involves the opening of

epoxide **141** by a vinylalane. This strategy is analogous to the conversion of **81** to **82** in Figure 15 (Scheme XV). Selective cleavage of the terminal monosubstituted double bond of monoterpene **146** by a suitably hindered, ligated OsO₄ species (such as ADmix- α) (Morikawa, K., *et al.*, *Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins*. J. Amer. Chem. Soc., 1993. **115**: p. 8463-8464; Andersson, P.G. and K.B. Sharpless, *A Dramatic Ligand Effect on the Relative REactivities of Substituted Alkenes with Osmium Tetroxide*. J. Amer. Chem. Soc., 1993. **115**: p. 7047-7048) in the presence of a reoxidant such as NaIO₄ should lead directly to the aldehyde **147**. Schroder, M., *Osmium Tetroxide Cis Hydroxylation of Unsaturated Systems*. Chem. Rev., 1980. **80**: p. 187-213. Its reduction to alcohol and protection as a TBS ether should be straightforward in providing **148**. Now, ozonolytic cleavage of the disubstituted terminal double bond of **148** should provide ketone **149** in one pot. Introduction of the vinyl iodide by Wittig reaction is precedented, giving the Z-iodide **150**. Now, metallation and in situ transmetallation with an alkyl aluminum chloride should give a vinyl alane intermediate, capable of opening epoxide **141** to give an aluminum alkoxide corresponding to **151**. *In situ* silylation of this intermediate should then give **151** in a one pot procedure starting from **150**. Finally, desilylative oxidation of the protected alcohol in **151** can be achieved by quinolinium fluorochromate to furnish the requisite aldehyde **152**. Chandrasekhar, S., K.P. Mohanty, and M. Takhi, *Practical One-Pot Di-O-silylation and Regioselective Deprotective Oxidation of 1-O-Silyl Ether in 1,2-Diols*. J. Org. Chem., 1997. **62**: p. 2628-2629. Now, aldol condensation as before with the trianion of **56a** should lead to production of **59**, which as before can be converted to Epothilone B.

A viable alternative to the iodide **150** of Figure 24 (Scheme XXIV) is shown in Figure 25 (Scheme XXV). The inexpensive industrial chemicals prenyl bromide and MVK can be coupled in one step with Zn/Cu accelerated sonochemically to furnish a well known phermone intermediate, **153**. Trehan, I.R., *et al.*, *Synthesis of undecan-3-one; (.+-.) frontalin; (.+-.)-endo-, and (.+-.)-exo-brevicommin under sonochemical aqueous conditions*. Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 1995. **34B**(5): p. 396-8. Wittig reaction of ketone **153** as before should then afford the Z-olefin **154**, chiral hydroboration of which is expected to smoothly give the alcohol-iodide **155**. Finally,

protection provides the common intermediate **150** (**148**, $R_1 = \text{TBS}$), also used in Scheme XXIV en route to Epothilone B.

A further scheme for synthesizing epothilones involves an intramolecular aldol condensation instead of the intermolecular approaches outlined above. Generation of the triene **156**:



is directly analogous to formation of the silylated derivative **132** except that the reaction is worked up with dilute acid instead of a silyl electrophile such as TBSOTf or TBSCl, giving the alcohol **156** instead. The β -lactone **157** (IR: 1832 cm^{-1}) was prepared directly from the keto-acid alcohol **56** by treatment with PhSO_2Cl and pyridine as shown in Figure 26a (Scheme XXVIa), and should serve as a source of acylating agent for construction of the triene-ketoalcohol construct **158**, as shown in Figure 26b (Scheme XXVIb). Thus, treatment of **156** with **157** in the presence of pyridine or other amines, with DMAP as catalyst, should allow for formation of **158** ($R = \text{H}$). Alternatively (step c in Scheme XXVIb), capture of the final alkoxide intermediate leading to **156** with **157**, instead of the water workup, should give **158** directly in a one pot procedure. Further, the product **158**, either purified, crude, or *in situ* (step c), can be O-alkylated with a variety of reagents such as benzyloxymethyl chloride (BOMCl), p-methoxybenzyloxymethyl chloride (PMBMCl), 2-trimethylsilylethyloxymethyl chloride (SEMCl) or even 3,4-dimethoxybenzyl chloride (DMBCl), bromide, or trichloroamidate ($\text{Ar-CH}_2\text{O-C}(\text{CCl}_3)=\text{NH}$). It can also be silylated with any usual silyl reagent such as TMS, TBS, TIPS, etc.

With protected **158** in hand, hydroboration as before with $(\text{lpc})_2\text{BH}$ can be followed by conventional workup to afford alcohol **159**, or the intermediate borane can be directly oxidized with Cr(VI) to afford the aldehyde **160**. Of course, the alcohol **159** can be oxidized under Swern conditions to furnish **160** as well. Now, selective enolborane formation with a dialkylboron triflate can be effected to give the transient boron enolate **160a** which should undergo intramolecular aldol reaction to afford the cyclized lactone **161**. Finally, removal of the protecting group with appropriate

conditions, e.g., when R = PMBM, use of DDQ readily leads to cleavage to deoxyepothilone B, **139**.

A variety of analogs of **60** can be prepared as outlined in Figure 27 (Scheme XXVII), taking advantage of the greater steric accessibility of the C-3 hydroxyl group. In one case, direct acylation of C-3 provides **162**, leaving only one additional hydroxyl group which could be acylated under more forced conditions to give **163**. Alternatively, silylation of C-3 furnishes **164**, and forced acylation then gives **165** after silica gel purification to simultaneously remove the TMS group from C-3. In these reactions, R = alkyl, aryl, alkyl-aryl, OR, NRR', SR, and so on. In addition, the X group in RCOX denotes the use of active esters to effect these transformations as well as acid chlorides, and in some cases may suggest the use of isocyanates, thioisocyanates, etc.

Another approach to producing analogs of epothilones was outlined in Figure 28 (Scheme XXVIII). Here, a generally applicable synthetic route to epothilones and their analogs is shown. The process entails the novel Normant reaction of a Grignard reagent **B** (where R can be H, Me or a variety of aryl, alkyl or other moieties) with a terminal alkyne **C** (where R can be H, Me or a variety of aryl, alkyl or other moieties); the resulting intermediate is then treated with an alkynyl lithium to produce an alkenyl-mixed cuprate **BC** which is quenched by a protected 1,2-epoxy-3-hydroxy species **A** (where R can be H, Me or a variety of aryl, alkyl or other moieties). The intermediate or crude product is then treated with an alcohol protecting group reagent (such as a SEM chloride, i.e. a 2-silylethoxymethoxy chloride), producing in a single operation, the diene **D**.

The diene **D** can either be hydroformylated under chiral conditions, or hydroborated using bis(isopinocampheyl)borane to furnish ultimately the aldehydes **E** or **F**. In the case of **F**, the PMB protecting group is removed, the alcohol is oxidized, and the ketone made to undergo Horner-Emmons reaction to install the vinylic aromatic species, such as **F**.

With either aldehyde **E** or **F**, aldol condensation of the dianion prepared from **10** followed by protection of the resulting aldol derived, β -hydroxy group as an acyl derivative (e.g. the TROC group; trichloroethoxycarbonyl or $\text{Cl}_3\text{CCH}_2\text{OCO}-$; or for example, a hexenoyl moiety; e.g. $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{CO}-$), leads to formation of the diastereomeric aldol adducts **G** or **H**. In the case of **H**, simple cleavage of the C-15 protecting group (when SEM, use a fluoride source such as $\text{HF}\cdot\text{pyridine}$) can be

achieved. After lactonization, the diprotected lactone **J** is obtained. Removal of the remaining silicon protecting group gives an epothilone D analog that can be epoxidized to give an epothilone B analog. Alternatively, norepothilone analogs that mirror the **H** manifold, **I**, can be obtained by derivatization of the C-16 hydroxyl group with R₇. As before, the silicon group can be removed to give a norepothilone D analog, epoxidation of which would give a norepothilone B analog.

In any case, R₁ can be **H** for the epothilone A series, or another group to provide an entirely new species.

After removal of the TBS group from **I** or **J**, an additional acyl group can be installed to give **K** or **L**. When the COR₃ group is a protecting group like a TROC, it can be removed from **K** or **L** to give **M** or **N**. These chemistries allow for the hydroxyl groups to be derivatized in any pattern desirable to achieve the required pharmacological properties of the materials. For example, in the case of **N**, when R₄, R₂, R₁, R = Me, R₃ = H, and R₆ = CH₂=CH(CH₂)₃CO-, an analog of epothilone is produced by total synthesis, but never via the natural product. The side-chain double bond can be selectively cleaved to allow formation of an aldehyde that can be used as a tether to solubilizing groups, etc.

As above, protecting groups can be manipulated to arrive at structures such as **M** with a variety of substituents. These substituents can be optimized by combinatorial or parallel synthesis methods to provide norepothilone analogs optimized for high anticancer potency and minimized toxicity. Additional approaches to targeting these analogs could involve tethering to carrier molecules.

In more detail, a specific example is provided in Figure 29 (Scheme XXIX). The Normant product **166** was protected as SEM ether to give **167**. The PMB group was deprotected by using DDQ and the resulting alcohol was oxidized to the corresponding ketone **169** which was then reacted with Horner-Emmons reagent **24** to furnish triene **170**. Hydroboration of compound **170** with bis(isopinocampheyl)borane and oxidative work up with hydrogen peroxide gave the *S*-methyl alcohol **171**. Oxidation of alcohol **171** afforded aldehyde **172**. The ensuing aldol condensation of **172** with ketoacid **10** gave products **173a** and **173b** in 1:1 ratio. Hydroxy acids are protected as TROC esters and SEM group was deprotected and subsequent macrolactonization afforded **174**. Removal of protecting groups gave desoxyepothilone B.

The particulars of Figure 29 (Scheme XXIX) allow for entry to previous Scheme XXVII (Figure 27), in which **178** is similar to **165**. Similarly, **174** can lead to the homolog of **164** in which the Si group is a TBS instead of a TMS. The TROC **165** can be acylated at C-3, and the TROC removed to give **162** and thereby **163**. This is shown in Figure 30 (Scheme XXX). An acyl group is installed at C3 of **178** to give **179**. The TROC can be removed to give **180**. Finally, another acyl group can be added to C7 to give a diacyl derivative **181**, itself available from the alternate manifold culminating in **184**. Along these lines, the TROC can be removed to afford **182** and the C7 hydroxy acylated to give **183**. Removal of the TBS group should give **184**.

A specific example is afforded in Figure 31 (Scheme XXXI), in which a hexenyl moiety is pendant to the C7 hydroxyl group. In this case, after the aldol reaction, the intermediate is quenched with hex-5-enoic acid active ester or the acid chloride to give **185**. This is similar to the TROC derivitization giving **173**. As before, selective SEM removal affords **186**. After lactonization, **187** is formed, from which the TBS can be removed with HF•pyridine to give **188**. Finally, the side chain olefin (least hindered) can be hydroxylated and cleaved affording the aldehyde **189**. Alternatively, a hexanoic acid ester derivative may instead be used, e.g. by replacing $\text{CH}_2=\text{CH}(\text{CH}_2)_3\text{COCl}$ in step a of Figure 31 with $\text{CH}_3(\text{CH}_2)_4\text{COCl}$ and leaving out steps e and f. The use of other alkanolic or alkenolic acid esters, substituted and unsubstituted, is also contemplated.

A further route to the epothilones is demonstrated with respect to Figures 32 through 37. The *Z* olefin, an essential feature for the synthesis of epothilone B, as reported in the literature, was prepared either by classical Wittig olefination methods or ring closing olefin metathesis approaches. Herein we report a unique and stereoselective method to generate the trisubstituted *Z* olefin geometry by modification of a classical Normant alkyne cupration and electrophile trap.

Retrosynthetic disconnection of epothilone B indicated to us that synthons **203** and **204** could serve as key intermediates, which could be coupled together via a double-diastereoselective aldol condensation, as shown in Figure 32 (Scheme XXXII) and macrolactonization to furnish the target framework. The synthesis of aldehyde unit **203**, the northern hemisphere of epothilone B, is based on the retrosynthetic strategy indicated in Figure 33 (Scheme XXXIII). Thus, ring opening of epoxide **205** by the Normant-derived vinyl cuprate **206**, should lead to an alcohol whose oxidation to ketone could be followed by a Wadsworth-Emmons olefination reaction. Finally, the α -methyl

carboxaldehyde could be generated by a chiral hydroboration-oxidation sequence to provide **203**.

The synthesis of fragment **203** was commenced by protection of (2*S*, 3*R*)-1,2-epoxy-3-butanol **208** as its *p*-methoxybenzyl (PMB) ether, as shown in Figure 34 (Scheme XXXIV). This was achieved by treating compound **208** with sodium hydride and PMB bromide to give **205** in 85% yield. Hetakeyama, S.; sakurai, K.; Takano, S. *Heterocycles*, **1986**, *24*, 633-637. The Normant coupling reaction with epoxide **205** was performed conveniently as follows. Normant, J. F. *Synthesis* 1972, 63-80; Marfat, M.; McGuirk, P.; R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888- 3092.

After forming the Grignard reagent from the reported bromide **209**, admission of CuBr-DMS complex and stirring for several hours at low temperature led to a black solution of cuprate reagent. Condensation of propyne (*g*) into the cuprate solution at low temperature was followed by addition of lithiohexyne. Alkylation of the resultant vinyl cuprate **210** was accomplished over the course of one day at -25 °C following addition of epoxide **205**. Chromatography of the crude product provided the diastereomerically pure *Z*-alkene **211** in 76% yield. The alcohol moiety of alkenol **211** was derivatized with SEMCl and DIPEA to provide a SEM-ether, **212**. Removal of the PMB ether of **212** with DDQ left the SEM-ether intact to give the alcohol **213**. Oxidation of **213** was then effected under Swern conditions to afford the methyl ketone **214** in 85% yield. Wadsworth-Emmons olefination of ketone **214** with the known phosphonate **207** led to the production of diastereomerically clean triene **215** in 72% yield. Schnizer, D.; Limberg, A.; Bohm, O. M. *Chem. Eur. J.* **1996**, *11*, 1477- 1482. Finally, diastereoselective hydroboration of the triene **215** using (*i*-PC)₂BH (Wifely, G.; Ayyangar, N. R.; Takashi Munekata.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 1076-1078; Brown, H. C.; Joshi, N. N. *J. Am. Chem. Soc.* **1988**, *53*, 4059- 4061) followed by oxidative work-up and subsequent Swern oxidation of the resulting alcohol **216**, furnished the enantiomerically pure aldehyde **203** in 92% yield.

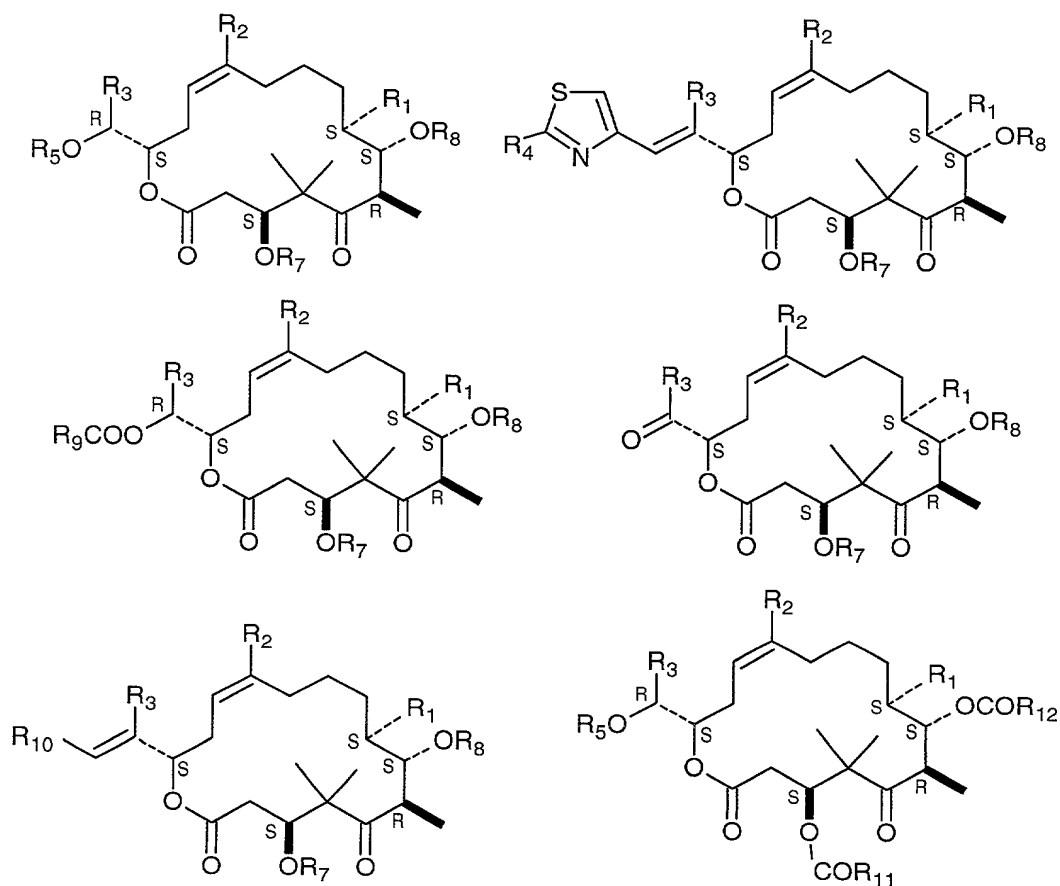
For the aldol condensation shown in Figure 32 (Scheme XXXII), the silyl protected keto-acid **204** was required. This acid could be prepared as reported in our work via an Evans enantioselective aldol condensation. Panicker, B.; Karle, J. M.; Avery, M. A. *Tetrahedron*, **2000**, *56*, 7859-7868 and references therein. As shown in Figure 35 (Scheme XXXV), the dibutylboron enolate of the reported oxazolidinone **217**

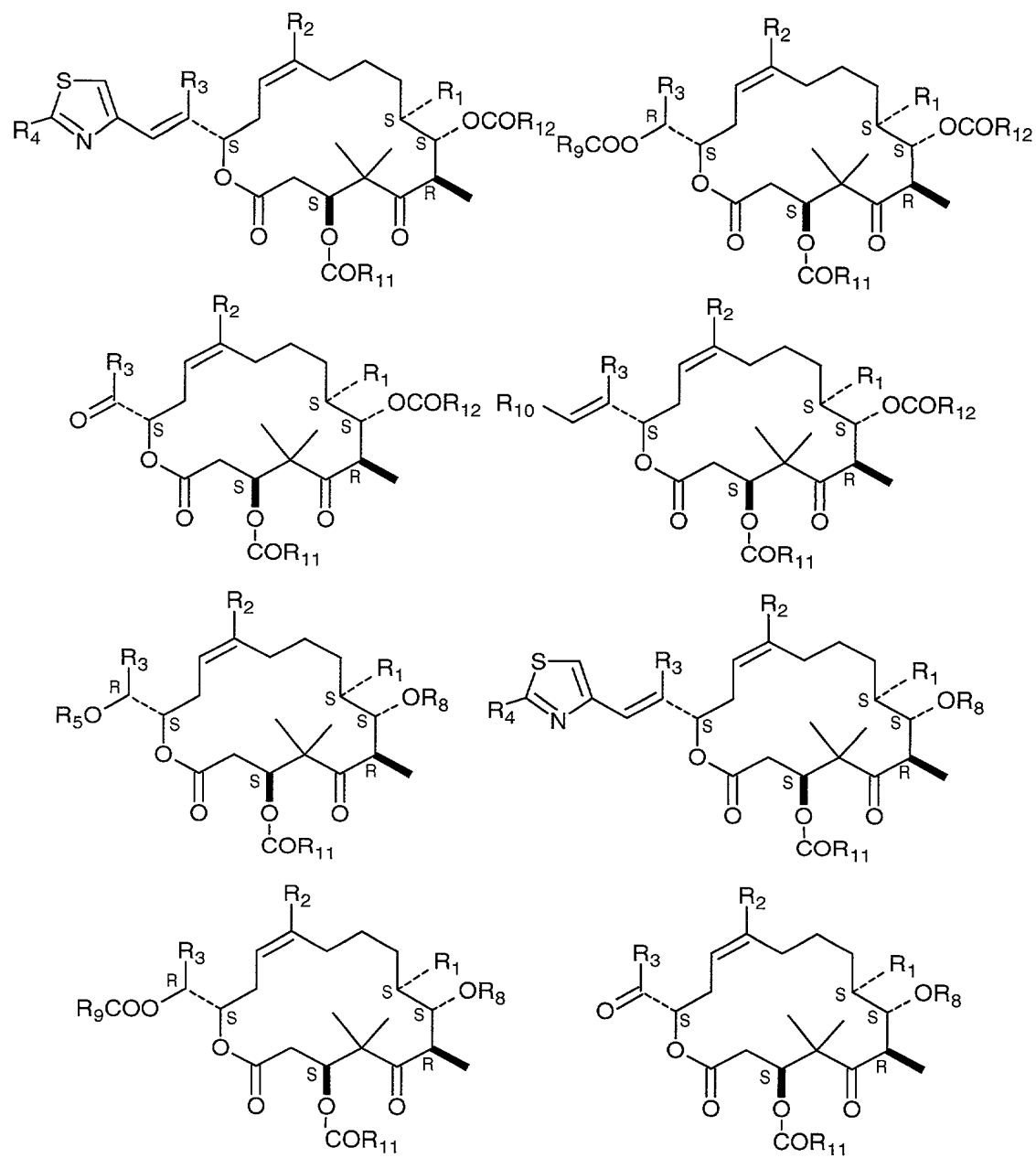
reacted with keto-aldehyde **218** to give an α -thiomethyl amide aldol intermediate. Desulfuration was readily accomplished using Raney Ni, providing the corresponding *R:S* aldol adducts **219** in a 23:77 ratio, respectively (70% yield). After silylation with TBDMSOTf and removal of auxiliary, we obtained **204** in good overall yield.

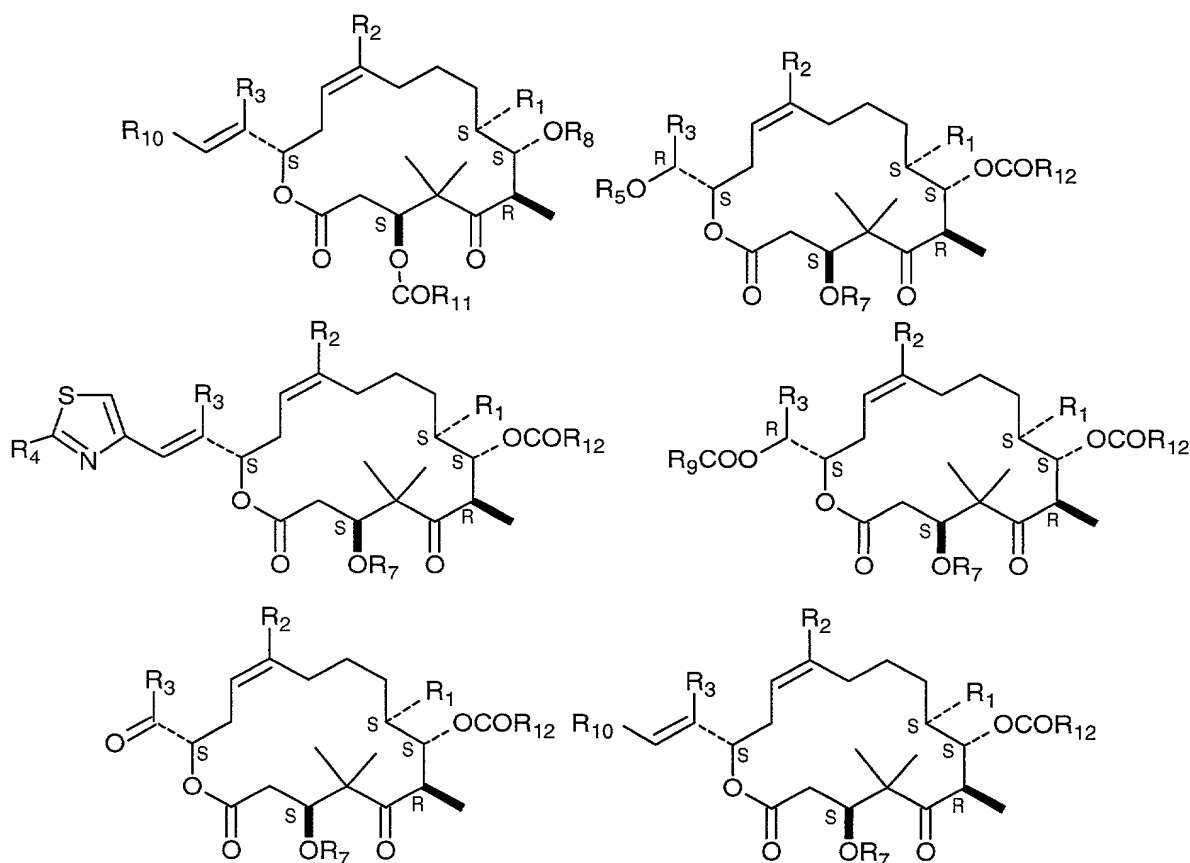
The optimum conditions for the aldol condensation of keto-acid **204** with aldehyde **203** required generation of the dilithio derivative of **204** with LDA (-78 °C to -40 °C) followed by metal exchange with anhydrous ZnCl₂ at -78 °C. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, F.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakaku, P.; Hamel, E. *Nature*, **1997**, *387*, 268- 272. Thereupon, reaction of aldehyde **203** with the transmetallated enolate of **204** led to formation of polar adducts best handled as shown in Figure 36 (Scheme XXXVI). Treatment of the aldol mixture with 1.2 equivalents of TBSCl and excess TrocCl in pyridine furnished a mixture of fully protected products. Upon exposure to trifluoroacetic acid at -20 °C, deprotection of the SEM ether with simultaneous deprotection of TBS esters occurred. At this stage the aldol product mixture could be conveniently separated from the unreacted keto-acid **204** by flash column chromatography giving adducts **220** and **221** in a 2:1 diastereomeric ratio.

The mixture of hydroxy acids was then subjected to macrolactonization using the Yamaguchi method (Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989) to obtain the corresponding lactones as shown in Figure 37 (Scheme XXXVII). The two lactones **222** and **223** were readily separated by flash column chromatography and **222** was characterized by conversion to natural product. Selective deprotection of the TBS group from **222** using HF-Py followed by chromatographic purification gave the desired Troc-alcohol **224**. Removal of the Troc group was effected using Zn and aq. NH₄Cl in MeOH to provide the diol **225**, epothilone D. Yang, D.; Wong, M.-K.; Yip, Y.-C.; *J. Org. Chem.* **1995**, *60*, 3887- 3889. Finally, treatment of **225** with methyl (trifluoromethyl)-dioxirane led cleanly to epothilone B **202**, whose properties were identical to reported spectral and physical data for the natural product. For synthetic Epothilone B **202**, $[\alpha]_D^{25} = -31^\circ$ (*c* 0.25, CHCl₃); Reported rotation (Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 100073-10092) for synthetic Epothilone B **2**, $[\alpha]_D^{25} = -31^\circ$ (*c* 0.045, CHCl₃).

While specific examples have been provided herein of particular chemical compounds formed by specific reaction steps, It should be appreciated that the present invention broadly contemplates numerous variations in the chemical compounds and in the reactants used in any given reaction step, thereby to form various chemical compounds having such substituents as might be desired, as understood by the ordinarily skilled person. For example, the present invention contemplates variations in the protecting groups, such as the use of other types and classes of protecting groups as generally understood by the ordinarily skilled organic chemist. Other variations contemplated by the present invention include variations in the ester moieties at the C-3 and C-7 positions, for example, as well as variations in the sidechain structures and substituents thereof. For example, the present invention broadly contemplates, without limitation, chemical compounds (and stereoisomers thereof) of the following formulas, among others:







wherein R_1 through R_{12} may be various substituents selected from the numerous varieties of known possible substituents in the art. For example, R_1 , R_2 , R_3 , R_4 , R_9 and R_{10} may be each selected from H, alkyl, alkenyl, alkynyl, aryl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, cycloalkyl, heterocyclo; R_5 , R_6 , R_7 and R_8 may be selected from H and a protecting group; and R_{11} and R_{12} may be each selected from alkyl, alkenyl, alkynyl, aryl, alkyl-aryl, alkyloxy, aryloxy, cycloalkyl, heterocyclo, amino, sulfo, and substitutions thereof. It is contemplated that R_{11} and R_{12} may be respectively selected such that the 3 and 7 positions may form various desired esters, and in particular esters of alkanolic and alkenolic acids, such as hexanoic and hexenoic acids (e.g., R_{11} or R_{12} may be $-(CH_2)_xCH_3$, $-(CH_2)_yCH=CH_2$, and the like where x and y are appropriate integers, such as 3 or 4. These substituents may be further substituted as understood in the art. It should further be understood that various appropriate intermediate compounds may thus be formed, such as precursors and compounds for use in, or formed during, the aldol condensation and macrolactonization steps described above, or in the various other conversion steps described herein.

Experimental

All solvents were purchased as reagent grade, and where appropriate were distilled from CaH₂ and stored over dry 4Å sieves for at least one day prior to use. Solvent and reagent transfers were accomplished via dried syringe, and all reactions were routinely conducted under an inert atmosphere unless otherwise indicated. Flash chromatography was accomplished using silica gel (Whatman 60, 230-400 mesh). Preparative thin-layer chromatography utilized 1-, 1.5-, or 2-mm-thick Analtech Uniplates with F-256, and 250-μm silica gel thin-layer chromatography plates were also purchased from Analtech. Unless otherwise noted, all NMR analyses were conducted in CDCl₃, on Bruker 300, 400, or 500 MHz instruments, and were referenced to chloroform at δ 7.27.

1-Trimethylsilyloxy-4-pentyne **13**:

To a solution of 4-pentyn-1-ol (25.0g, 0.30 mole) in dry CH₂Cl₂ (250 ml) at 0°C, was added imidazole (40.46g, 0.60 mole) and chlorotrimethylsilane (56.6 ml, 0.45 moles) and stirred for 2h. The reaction mixture was diluted with water and extracted with CH₂Cl₂ (3 x 100 ml). Combined organic extracts were washed with water, brine, dried (Na₂SO₄) and the solvent was evaporated. Purification of the crude product by vacuum distillation afforded the pure ether **13** (44.1g, 95%).

¹H NMR (300 MHz CDCl₃): δ 3.64 (t, J = 5.1 Hz, 2H), 2.24 (t, J = 4.6 Hz, 2H), 1.90 (s, 1H), 1.68-1.72 (tt, J = 13.2, 6.2 Hz, 2H), 0.09 (s, 9H).

¹³C NMR (100 MHz CDCl₃): δ 83.9, 68.2, 60.7, 31.2, 14.7, -0.7

Silyloxyepoxide **59**:

To a solution of the corresponding epoxy alcohol (10.01g, 113.6 mmol) in dry CH₂Cl₂ (100 ml) at 0°C, was added TBDMSCl (24.8g, 164.8 mmol) and imidazole (15.46g, 227.2 mmol) and the mixture was stirred for 4 h. The reaction mixture was diluted with water and extracted with EtOAc (3 x 80 ml). Combined organic extracts were washed with water, brine, dried (Na₂SO₄) and the solvent was evaporated. Purification on silica gel column chromatography (20% EtOAc in hexanes) furnished epoxide **5a** (20.6g, 90%).

¹H NMR (300 MHz CDCl₃): δ 3.72-3.68 (m, 1H), 2.82-2.80 (m, 1H), 2.69-2.61 (m, 2H), 1.20 (dd, J = 8.2, 1.9 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 67.5, 55.5, 44.5, 25.6, 20.7, 18.0, -4.9, -5.0

Diol 15a: Opening of the epoxide and hydrolysis:

To a stirred solution of pentyne **13** (10.76g, 69 mmol) in dry toluene (200 ml) at 0° C, n-BuLi (2.5 M solution in hexane, 69 mmol) was added and stirred for 15 min. Subsequently dimethylaluminum chloride solution (1.0 M in hexane, 69 mmol) was added and further stirred for 45 min at the same temperature. The oxirane **5a** (7.0g, 34.5 mmol) in toluene (5 ml) was added and the mixture was allowed to warm to room temperature and stirred at RT for 3 hr. The reaction mixture was carefully quenched by addition of saturated Na₂SO₄ solution and the slurry obtained was filtered through a pad of celite and washed with EtOAc. The filtrate was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude residue obtained was dissolved in H₂O:acetic acid (1:3) mixture, stirred for 30 min at room temperature, diluted with water and extracted with EtOAc (3 x 100 ml). The organic phase was washed with water, brine, dried and the solvent was removed. Acetic acid was removed by repeated evaporations with hexane. The residue was purified by flash column chromatography on silica gel to furnish diol **15a** (7.9g, 80%).

¹H NMR (400 MHz CDCl₃): δ 3.81 (dq, J = 11.4, 6.0 Hz, 1H), 3.71 (t, J = 6.0 Hz, 2H), 3.55 (dt, J = 12.0, 6.3 Hz, 1H), 2.38-2.30 (m, 2H), 2.29-2.21 (m, 2H), 1.71 (tt, J = 13.0, 6.6 Hz), 1.11 (d, J = 6.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

¹³C NMR (100 MHz CDCl₃): δ 82.1, 77.2, 74.6, 70.7, 61.7, 31.8, 26.1, 23.3, 18.8, 18.3, 15.7, -4.1, -4.5.

Partial hydrogenation of the diol 15a:

A mixture of diol **15a** (7.5g, 26 mmol), quinoline (6.2 ml, 52 mmol) and Lindler catalyst (1.125g) in ethanol (75 ml), were stirred under H₂ atmosphere and the reaction was carefully monitored by TLC. Upon completion, the contents were filtered through celite and the filtrate was concentrated. The residue was dissolved in ether (200 ml) and washed with 2% HCl to remove quinoline. The organic phase was further washed with water, 5% NaHCO₃ solution, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography over silica gel gave the diol **16a** (7.25g, 96%).

¹H NMR (400 MHz CDCl₃): δ 5.41-5.37 (m, 2H), 3.68-3.65 (m, 1H), 3.53-3.51 (m, 1H), 3.46-3.41 (dt, J = 8.6, 4.2 Hz, 1H), 2.20-2.07 (m, 2H), 2.05-2.00 (m, 2H), 1.59-1.47 (m, 2H), 1.04 (d, J = 6.1 Hz, 3H), 0.81 (s, 9H), -1.2 (s, 3H), -2.9 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 131.9, 126.8, 75.6, 71.5, 61.6, 32.2, 30.6, 26.2, 23.7, 18.3, 17.9, -4.1, -4.5.

Iodide 17a: Monotosylation, Silylation and the iodination sequence:

To a solution of the diol **16a** (6.21g, 21.52 mmol) in dry CH₂Cl₂ (60 ml) at 0°C, was added tosyl chloride (4.93g, 25.83 mmol), pyridine (3.5 ml, 43.1 mmol) and catalytic amount of DMAP. The reaction mixture was allowed to warm to room temperature and stirred for overnight. Water was added to the reaction mixture and extracted with EtOAc (3 X 60 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography over silica gel afforded the monotosylate (7.62g, 80%).

¹H NMR (400 MHz CDCl₃): δ 7.78 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.50-5.35 (m, 2H), 4.03 (t, J = 6.4 Hz, 2H), 3.80-3.74 (m, 1H), 3.51-3.50 (m, 1H), 2.44 (s, 3H), 2.14-2.07 (m, 4H), 1.71 (tt, J = 14.0, 6.6 Hz, 2H), 1.08 (d, J = 6.3 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 145.1, 133.6, 130.24, 130.2, 128.2, 127.7, 75.4, 71.3, 70.3, 30.5, 29.1, 26.2, 23.6, 22.0, 18.4, 17.7, -4.0, -4.5.

A mixture of monotosylate (8.34g, 18.8 mmol), 2,6-lutidine (3.8 ml, 33.0 mmol) and TMSOTf (4.3 ml, 23.6 mmol) in dry CH₂Cl₂ (50 ml) at 0°C, was stirred while allowing the temperature to rise to room temperature. After stirring at RT for 2 h water was added and extracted into EtOAc (3 X 60 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography on silica gel impregnated with triethylamine afforded the pure bis silyl ether (9.36g, 99%).

¹H NMR (400 MHz CDCl₃): δ 7.78 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 5.47-5.41 (m, 1H), 5.36-5.30 (m, 1H), 4.03 (t, J = 6.6 Hz, 2H), 3.66-3.60 (m, 1H), 3.47-3.42 (m, 1H), 2.45 (s, 3H), 2.26-2.2 (m, 1H), 2.11-2.04 (m, 3H), 1.70 (tt, J = 14.1, 7.1 Hz, 2H), 1.08 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 145.0, 133.7, 130.2, 129.4, 128.7, 128.3, 77.8, 72.2, 70.4, 31.8, 29.2, 26.3, 26.2, 23.7, 22.0, 19.8, 18.5, 0.97, -4.0, -4.2.

A mixture of the bis silyl ether obtained above (9.03g, 18.0 mmol) and NaI (6.74g, 45.0 mmol) in dry acetone (90 ml), was heated under reflux for 2h. Removal of the solvent under reduced pressure and purification of the product by flash column chromatography on silica gel to give the pure iodide **17a** (7.37g, 87%).

¹H NMR (400 MHz CDCl₃): δ 5.5-5.48 (m, 1H), 3.67-3.64 (m, 1H), 3.50-3.46(m, 1H), 3.18 (t, J = 7.0 Hz, 2H), 2.32-2.29 (m, 1H), 2.2-2.12 (m, 3H), 1.90 (tt, J = 14.2, 7.1 Hz, 2H), 1.12 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 9H), 0.04 (s, 6H).

¹³C NMR (100 MHz CDCl₃): δ 129.3, 128.8, 100.0, 77.9, 72.2, 33.8, 32.1, 28.6, 26.4, 19.9, 18.6, 6.9, 1.1, -3.9, -4.2.

Bissilyloxyiodide 17b:

Conversion of the diol **16b** employing the same reaction sequence described above yielded the iodide **17b**.

¹H NMR (400 MHz CDCl₃): δ 7.75-7.68 (m, 4H), 7.42-7.3 (m, 6H), 5.49-5.33 (m, 2H), 3.76 (dq, J = 6.1 Hz, 1H), 3.61 (dt, J = 7.9, 4.2 Hz, 1H), 3.16 (t, J = 6.9 Hz, 2H), 2.38-2.19 (m, 2H), 2.18-2.05 (m, 2H), 1.4-1.32 (m, 2H), 1.09 (s, 9H), 1.01 (d, J = 6.2 Hz, 3H), 0.10 (s, 9H).

¹³C NMR (100 MHz CDCl₃): δ 136.4, 136.4, 135.2, 134.3, 129.9, 129.8, 129.3, 128.7, 127.9, 127.8, 77.7, 73.3, 33.8, 31.9, 28.6, 27.5, 19.7, 19.5, 6.8, 1.0.

HydroxybisMEMether 22: Bisetherification and desilylation of 16a:

To a solution of the diol **16a** (7.0 g, 24.3 mmol) in dry CH₂Cl₂ (100 ml) at 0°C, was added DIPEA (21.0 ml, 120 mmol) and MEMCl (13.9 ml, 120 mmol) and stirred for 1h. The reaction was quenched by the addition of saturated NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 60 ml). The combined organic extracts were washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography using silica gel gave corresponding bis MEM ether (10.4g, 92%).

¹H NMR (400 MHz CDCl₃): δ 5.42-5.46 (m, 2H), 4.81 (d, J = 7.5 Hz, 1H), 4.75 (d, J = 7.5 Hz, 1H), 4.70 (s, 2H), 3.67-3.80 (m, 5H), 3.56-3.51 (m, 6H), 3.39 (s, 3H), 3.38 (s, 3H), 2.26-2.23 (m, 2H), 2.10-2.08 (m, 2H), 1.66-1.62 (m, 3H), 1.12 (d, J = 6.2 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 131.1, 127.0, 95.8, 95.5, 81.7, 72.2, 70.5, 67.6, 67.4, 67.0, 59.3, 29.9, 29.3, 26.2, 24.4, 19.1, 18.4, 14.5, -4.2, -4.4.

To a solution of the bis MEM ether obtained above (9.5g, 20.4 mmol) in THF (100 ml) at 0°C was added TBAF (1.0 M solution in THF, 41 mmol) and the mixture was at room temperature for overnight. Diluted with water and extracted with EtOAc (3 x 100 ml). The combined organic extracts were washed with brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography on silica gel gave **22** (6.16g, 86%).

¹H NMR (400 MHz CDCl₃): δ 5.48-5.41 (m, 2H), 4.80 (d, J = 7.2 Hz, 1H), 4.74 (d, J = 7.2 Hz, 1H), 4.70 (s, 2H), 3.85-3.80 (m, 2H), 3.79-3.66 (m, 3H), 3.58-3.53 (m, 7H), 3.39 (s, 3H), 3.38 (s, 3H), 2.35-2.28 (m, 2H), 2.22-2.209 (m, 3H), 1.64 (tt, J = 13.9, 6.8 Hz, 2H), 1.16 (d, J = 6.5 Hz, 3H).

¹³C NMR (100 MHz CDCl₃): δ 131.1, 126.5, 95.8, 95.5, 83.5, 71.94, 71.9, 68.6, 67.4, 67.3, 66.8, 59.0, 29.7, 28.7, 24.1, 17.7.

Ketobisether 23: Swern oxidation of the alcohol 22:

DMSO (9.0 ml, 127.2 mmol) was added to a solution of oxalyl chloride (12.91g, 101.72 mmol) in CH₂Cl₂ (60 ml) at -78°C and stirred for 15 min. The alcohol **22** (5.94g, 17.0 mmol) in CH₂Cl₂ was added slowly and stirring was continued for 2 h. Triethylamine was added and the temperature was allowed to rise to RT. Quenched with water, extracted with methylene chloride, washed with water, dried (Na₂SO₄) and the solvent evaporated. Purification of the crude product by chromatography over silica gel (70% ethylacetate in hexanes) yielded the pure ketone **23** (4.37g, 74%).

¹H NMR (400 MHz CDCl₃): δ 5.54-5.48 (m, 1H), 5.42-5.36 (m, 1H), 4.8 (d, J = 7.0 Hz, 1H), 4.72 (d, J = 7.0 Hz, 1H), 4.7 (s, 2H), 4.07 (t, J = 6.2 Hz, 1H), 3.74-3.66 (m, 4H), 3.56-3.50 (m, 6H), 3.39 (s, 3H), 3.37 (s, 3H), 2.45 (t, J = 6.6 Hz, 2H), 2.17 (s, 3H), 2.11 (q, J = 7.4 Hz, 2H), 1.62 (tt, J = 14.0, 6.7 Hz, 2H).

¹³C NMR (100 MHz CDCl₃): δ209.4, 132.5, 124.3, 95.6, 95.3, 82.2, 72.0, 71.9, 67.7, 67.3, 66.9, 59.1, 30.0, 29.6, 26.7, 24.2.

Thiazole 25: Horner-Emmons reaction of the ketone 23:

To a solution of the phosphonate **24** (5.6g, 22.5 mmol) in dry THF (100 ml) at -78° C, was added n-BuLi (2.5 M solution in hexane, 0.95 equiv.) and stirred for 45 min. Subsequently, ketone **23** (3.93g, 11.25 mmol) in THF (5 ml) was added and stirred for 1h at -78 C and then slowly allowed to warm to room temperature and left overnight. The reaction was quenched by the addition of saturated NH₄Cl solution and extracted with EtOAc (3 x 60 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography on silica gel furnished the pure compound **25** (3.85g, 77%).

¹H NMR (400 MHz CDCl₃): δ6.84 (s, 1H), 6.38 (s, 1H), 5.35-5.31 (m, 2H), 4.61 (d, J = 6.9 Hz, 1H), 4.59 (s, 2H), 4.53 (d, J = 6.9 Hz, 1H), 4.0 (t, J = 6.8 Hz, 1H), 3.74-3.7 (m, 2H), 3.59-3.56 (m, 2H), 3.52-3.50 (m, 1H), 3.48-3.41 (m, 6H), 3.28 (s, 3H), 3.27 (s, 3H), 2.59 (s, 3H), 2.34-2.30 (m, 1H), 2.28-2.25 (m, 1H), 2.02 (q, J = 6.7 Hz, 2H), 1.91 (s, 3H), 1.57-1.50 (tt, J = 14.3, 6.7 Hz, 2H).

¹³C NMR (100 MHz CDCl₃): δ164.8, 153.1, 138.6, 131.3, 126.3, 121.8, 116.3, 95.8, 93.0, 81.9, 72.13, 72.11, 67.6, 67.3, 67.0, 59.3, 32.2, 29.9, 24.4, 19.5, 14.1

Diol 26: Deprotection of the bisether 25:

A mixture of **25** (3.7g, 8.34 mmol), THF (30 ml) and 9.0 N HCl were stirred at room temperature for overnight. The reaction mixture was carefully neutralized by addition of 10 % NaHCO₃ solution and extracted with EtOAc (3 x 60 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography on silica gel (90% EtOAc in hexanes) furnished the diol **26** (1.34g, 60%).

¹H NMR (400 MHz CDCl₃): δ 6.8 (s, 1H), 6.5 (s, 1H), 5.43-5.32 (m, 2H), 4.11 (t, J = 5.1 Hz, 3.54-3.49 (m, 2H), 2.61 (s, 3H), 2.42-2.35 (m, 2H), 2.31-2.26 (m, 2H), 2.19-2.13 (m, 2H), 2.07-2.02 (m, 2H), 1.9 (s, 3H), 1.59-1.49 (m, 2H).

¹³C NMR (100 MHz CDCl₃): δ165.1, 153.0, 142.7, 132.0, 126.5, 118.9, 115.6, 115.56, 77.1, 61.5, 33.7, 32.2, 23.9, 19.3, 14.9.

Silyloxyiodide 27: Monotosylation, silylation and iodination sequence:

To a solution of the diol **26** (2.25g, 8.4 mmol) in dry CH₂Cl₂ (20 ml) at 0°C, was added tosyl chloride (1.93g, 10.0 mmol), pyridine (1.36 ml, 16.8 mmol) and catalytic amount of DMAP and the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and extracted with EtOAc (3 x 40 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography over silica gel afforded the corresponding monotosylate (2.83g, 82%).

¹H NMR (400 MHz CDCl₃): δ 7.74 (d, J = 8.3 Hz, 2H), 7.3 (d, J = 8.3 Hz, 2H), 6.9 (s, 1H), 6.5 (s, 1H), 5.40-5.36 (m, 2H), 4.12 (t, J = 6 Hz, 1H), 3.99 (t, J = 6.4 Hz, 2H), 2.66 (s, 3H), 2.40 (s, 3H), 2.30 (t, J = 6.3 Hz, 2H), 2.05 (dd, J = 14.4, 7.4 Hz, 2H), 1.97 (s, 3H), 1.66 (tt, J = 14.2, 7.4 Hz, 2H).

¹³C NMR (100 MHz CDCl₃): δ 165.0, 153.1, 145.1, 142.0, 133.5, 130.6, 130.3, 128.3, 127.3, 119.4, 115.9, 77.9, 70.3, 33.6, 29.1, 23.7, 22.0, 19.5, 14.7.

To a solution of the monotosylate obtained above (2.14g, 5.23 mmol) in dry CH₂Cl₂ (30 ml) at 0°C, was added 2,6-lutidine (1.07 ml, 9.14 mmol) and TBSOTf (1.5 ml, 6.53 mmol), the reaction was allowed to warm to room temperature and stirred for 2h at RT. Diluted with water and extracted with EtOAc (3 x 60 ml). The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. Purification by flash column chromatography on silica gel afforded the corresponding silylether (2.74g, 98%)

¹H NMR (400 MHz CDCl₃): δ 7.75 (d, J = 6.54 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 6.90 (s, 1H), 6.43 (s, 1H), 5.42-5.38 (m, 2H), 5.30-5.25 (m, 1H), 4.09 (t, J = 6.3 Hz, 1H), 3.99 (t, J = 6.5 Hz, 2H), 2.68 (s, 3H), 2.4 (s, 3H), 2.31-2.17 (m, 2H), 2.08-2.0 (m, 2H), 1.95 (s, 3H), 1.70-1.63 (tt, J = 13.9, 6.9 Hz, 2H), 0.84, (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 164.8, 153.5, 145.1, 142.3, 133.6, 130.2, 129.4, 128.3, 128.0, 119.3, 115.6, 78.8, 70.4, 35.0, 29.2, 26.3, 23.7, 22.0, 19.6, 18.6, 14.3, -4.25, -4.55.

A solution of the silylether obtained above (1.56g, 2.92 mmol) in dry acetone (25 ml), was added NaI (1.09g, 7.3 mmol) and the mixture was heated under reflux for 2h. The solvent was removed under reduced pressure and the crude product obtained was

purified by flash column chromatography on silica gel to give the iodide **27** (1.29g, 90%).

¹H NMR (400 MHz CDCl₃): δ 6.85 (s, 1H), 6.40 (s, 1H), 5.41-5.28 (m, 2H), 4.08 (t, J = 6.3 Hz, 1H), 3.11-3.06 (m, 2H), 2.62 (s, 3H), 2.27 (dt, J = 12.9, 6.7 Hz, 2H), 2.06 (dt, J = 13.8, 6.8, 2H), 1.95 (s, 3H), 1.80 (tt, J = 14.0, 6.9 Hz, 2H), 0.83 (s, 9H), 0.0 (s, 3H), -0.05 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 164.2, 153.0, 141.9, 141.85, 128.9, 127.6, 118.8, 115.0, 78.4, 34.7, 33.3, 28.1, 25.8, 19.2, 18.1, 13.9, 6.3, -4.7, -5.0.

Alkylation of the iodide **17b** with the sultam **18**:

To a stirred solution of the sultam **18** (4.065g, 15 mmol) in THF was added n-BuLi (1.056g, 16.5 mmol) at -78°C over a period of one hour. The resulting mixture was stirred further at -78°C for one hour and a mixture of the iodide **17b** (9.801g, 16.5 mmol) and HMPA (5.376g, 30 mmol) was slowly added. The reaction temperature was allowed to raise to -20°C and stirring was continued at that temperature for 4 h. Quenched with saturated NH₄Cl solution and extracted with EtOAc. The organic layer was washed with water, brine, dried (Na₂SO₄) and the solvent evaporated. The crude product obtained was purified by chromatography over silica gel (10% ethylacetate in hexanes) to afford the adduct **19b** (4.348g, 59%).

¹H NMR (400 MHz CDCl₃): δ 7.72-7.68 (m, 4H), 7.44-7.32 (m, 6H), 5.40-5.28 (m, 2H), 3.89 (t, J = 6.2 Hz, 1H), 3.74 (dq, J = 6.1, 3.9 Hz, 1H), 3.57 (dt, J = 7.9, 4.2 Hz, 1H), 3.46 (q, J = 13.7 Hz, 2H), 3.15-3.03 (m, 1H), 2.30-2.20 (m, 1H), 2.19-2.09 (m, 1H), 2.08-2.02 (m, 2H), 2.02-1.92 (m, 2H), 1.93-1.82 (m, 3H), 1.78-1.62 (m, 1H), 1.50-1.25 (m, 4H), 1.16 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.07 (s, 9H), 1.02 (d, J = 7.1 Hz, 3H), 0.08 (s, 9H).

¹³C NMR (100 MHz CDCl₃): δ 176.9, 136.4, 136.3, 135.2, 134.3, 131.2, 129.9, 129.8, 127.9, 127.7, 127.2, 77.8, 73.3, 65.6, 53.6, 48.6, 48.1, 45.1, 40.2, 39.0, 35.5, 33.3, 31.9, 27.6, 27.5, 27.3, 26.8, 21.2, 20.3, 19.7, 19.3, 17.0, 1.0.

Alkylation of the iodide **17a** with the sultam **18**:

The alkylation was carried out as outlined above to yield the adduct **19a** in 65% yield.

¹H NMR (400 MHz CDCl₃): δ 5.42-5.32 (m, 2H), 3.88 (dd, J = 6.9, 5.4 Hz, 1H), 3.68-3.60 (m, 1H), 3.45 (q, J = 13.7 Hz, 2H), 3.48-3.42 (m, 1H), 3.10-3.02 (m, 1H), 2.4-2.3

(m, 1H), 2.12-1.96 (m, 5H), 1.92-1.82(m, 3H), 1.75-1.65 (m, 1H), 1.50-1.25 (m, 5H), 1.15 (s, 3H), 1.14 (d, J = 7 Hz, 3H), 1.92 (d, J = 6.1 Hz, 3H), 0.96 (s, 3H), 0.87 (s, 9H), 0.08 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz CDCl_3): δ 176.9, 131.1, 127.2, 77.9, 72.1, 65.6, 53.5, 48.5, 48.0, 45.0, 40.2, 39.0, 35.4, 33.2, 32.0, 27.7, 27.3, 26.8, 26.3, 21.2, 20.3, 19.7, 18.5, 17.0, 1.0, -3.9, -4.2

Alkylation of the iodide 27 with the sultam 18:

The alkylation was carried out as outlined above to yield the adduct **28** in 68% yield.

^1H NMR (400 MHz CDCl_3): δ 6.8 (s, 1H), 6.4 (s, 1H), 5.38-5.28 (m, 2H), 4.08 (t, J = 6.3 Hz, 1H), 3.85 (t, J = 5.8 Hz, 1H), 3.42 (q, J = 13.2 Hz, 2H), 3.10-3.02 (m, 1H), 2.6 (s, 3H), 2.32-2.22 (m, 2H), 2.50-1.98 (m, 3H), 1.96 (s, 3H), 1.85-1.80 (m, 2H), 1.72-1.62 (m, 1H), 1.48-1.20 (m, 6H), 1.12 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 0.92 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (100 MHz CDCl_3): δ 176.8, 164.7, 153.4, 142.6, 131.1, 126.6, 119.1, 115.4, 78.9, 65.6, 53.5, 48.5, 48.0, 45.0, 40.1, 39.0, 35.4, 35.0, 33.2, 27.6, 27.3, 26.8, 26.2, 21.2, 20.2, 19.5, 18.5, 16.9, 14.2, -4.2, -4.5.

Aldehyde 20b: Reductive cleavage of the adduct 19b:

To a solution of the adduct (3.685g, 5 mmol) in 1:1 mixture of THF and CH_2Cl_2 (50 ml) at -78°C was added DIBAH (1.209g, 8.5 mmol) in CH_2Cl_2 . The reaction mixture was warmed to -20°C , stirred at that temperature for 1hr and quenched with saturated Na_2SO_4 solution. The slurry obtained was filtered through a pad of celite, washed with EtOAc. Evaporation of the filtrate gave the crude product, which was purified by chromatography over silica gel (5% ethylacetate in hexanes) to furnish the pure aldehyde **20b** (1.7816g, 68%).

^1H NMR (400 MHz CDCl_3): δ 9.62 (d, J = 1.9 Hz, 1H), 7.78-7.70 (m, 4H), 7.47-7.35 (m, 6H), 5.48-5.33 (m, 2H), 3.81 (dq, J = 6.1, 6.0 Hz, 1H), 3.64 (dt, J = 8, 4.3 Hz, 1H), 2.39-2.30 (m, 2H), 2.30-2.20 (m, 1H), 2.10-2.03 (m, 2H), 1.78-1.68 (m, 1H), 1.48-1.32 (m, 3H), 1.15-1.1(m, 12H), 1.04 (d, J = 6.2 Hz, 3H), 0.13, (s, 9H).

^{13}C NMR (100 MHz CDCl_3): δ 205.3, 136.4, 136.4, 135.2, 134.4, 131.0, 129.9, 129.9, 127.9, 127.8, 127.6, 77.8, 73.3, 46.6, 31.9, 30.5, 27.7, 27.5, 27.3, 27.3, 19.7, 19.4, 13.7, 1.05.

Aldehyde 20a: Reductive cleavage of the adduct 19a:

The reduction of the adduct **19a** was carried out as described above to yield the aldehyde **20a** in 71% yield.

^1H NMR (400 MHz CDCl_3): δ 9.60 (d, J = 1.9 Hz, 1H), 5.45-5.35 (m, 2H), 3.64 (dq, J = 5.9, 5.1 Hz, 1H), 3.46 (dt, J = 7.8, 4.5 Hz, 1H), 2.38-2.25 (m, 2H), 2.15-2.09 (m, 1H), 2.08-2.02 (m, 2H), 1.75-1.66 (m, 1H), 1.45-1.32 (m, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.1 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz CDCl_3): δ 205.2, 130.9, 127.6, 77.9, 77.1, 72.1, 46.5, 32.0, 30.5, 27.7, 27.2, 26.3, 19.8, 18.5, 13.6, 0.99, -3.9, -4.2.

Aldol reaction of the sultam 51 with the aldehyde 9:

To a solution of the acetylsultam **51** (5.02g, 19.5 mmol) in dry CH_2Cl_2 (35 ml) at 0°C , DIPEA (4.1 ml, 23.4 mmol) and dibutylborontriflate (1.0 M solution in CH_2Cl_2 , 21.5 mmol) were added and stirred for 30 min. The reaction mixture was cooled to -78°C and the keto aldehyde **9** (2.5g, 19.5 mmol) in CH_2Cl_2 (5 ml) was added and stirring was continued for 1h. The reaction mixture was then allowed to warm to room temperature and quenched by addition of p^{H} 7.0 buffer solution and extracted with EtOAc (3 x 60 ml). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and the solvent evaporated. The residue was taken in methanol (40 ml), cooled to 0°C and 30 % H_2O_2 (5.0 ml) was added and stirred for 1h. The reaction mixture was diluted with water and extracted with EtOAc (3 x 60 ml), washed with brine, dried (Na_2SO_4). Evaporation of the solvent and purification of the crude product using flash chromatography over silica gel (15% EtOAc in hexanes) resulted in the β -hydroxy adduct **52** (3.9g, 61%).

^1H NMR (300 MHz CDCl_3): δ 4.38-4.32 (m, 1H), 3.92-3.89 (m, 1H), 3.51 (d, J = 13.8 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.28 (d, J = 4.3 Hz, 1H), 2.90 (dd, J = 15.6, 2.2 Hz, 1H), 2.80-2.72 (m, 1H), 2.62-2.58 (m, 2H), 2.22-2.12 (m, 1H), 2.10-2.05 (m, 1H), 1.92-1.85 (m, 3H), 1.45-1.31 (m, 2H), 1.20 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz CDCl_3): δ 216.1, 171.6, 73.1, 63.5, 53.3, 51.5, 48.9, 48.1, 45.1, 39.1, 38.8, 33.2, 31.5, 26.8, 23.3, 21.9, 20.2, 19.6, 8.3.

Keto acid 10: Silylation and hydrolysis of the adduct 52:

To a mixture of the adduct **52** (2.18g, 5.7 mmol) in dry CH₂Cl₂ (40 ml) at 0°C, was added 2,6-lutidine (1.3 ml, 11 mmol) and TBDMSOTf (1.95 ml, 8.5 mmol). The reaction mixture was allowed to warm to room temperature and stirred for a period of 3h. Water was added to the reaction mixture and extracted with EtOAc (3 x 30 ml). Combined organic extracts were washed with water, brine, dried (Na₂SO₄) and the solvent was evaporated. Purification by flash chromatography over silica gel (5% EtOAc in hexanes) gave the corresponding silylated adduct (2.54g, 90%).

To a solution of silylated adduct obtained above (1.95g, 3.9 mmol) in H₂O: THF (1:3), was added 30% H₂O₂ (3.0 ml, 7.0 equiv.) and LiOH•H₂O (0.327g, 7.8 mmol) and stirred at ambient temperature for 6h. Water was added to the reaction mixture and extracted with EtOAc. The aqueous phase was acidified with 2.0 N HCl, and extracted into EtOAc (3 x 50 ml). Combined organic extracts were washed with water, brine, dried (Na₂SO₄) and the solvent was evaporated. Purification by flash column chromatography over silica gel (20% ether in hexanes) furnished the acid **10** (0.74g, 63%).

¹H NMR (400 MHz CDCl₃): δ 4.46 (dd, J = 6.8, 3.7 Hz, 1H), 2.60-2.46 (m, 3H), 2.32 (q, J = 6.9 Hz, 2H), 1.14 (s, 3H), 1.09 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 215.5, 73.9, 53.0, 39.6, 32.2, 26.3, 21.5, 20.9, 18.5, 8.1, -4.0, -4.5.

Aldol condensation of the acid 34 with aldehyde 20a:

To a solution of LDA in THF (5 ml) at -78°C [generated from n-BuLi (155 mg, 2.42 mmol) and DIPA (2.67 mg, 2.64 mmol)] was added the acid **34** (0.332g, 1.1 mmol) in THF. Temperature was allowed to raise to -30°C and stirred at that temperature for 45 min. Aldehyde **20a** (0.400g, 1 mmol) in THF was added and the reaction mixture was stirred at -78°C for 1hr. Quenched with saturated ammonium chloride solution and extracted with ethylacetate. The organic layer was washed with water, brine, dried (Na₂SO₄) and solvent evaporated to give a crude product which was used for the next step without further purification.

To a solution of crude product obtained from the previous reaction in CH₂Cl₂ (5 ml) at 0°C was added 2,6-lutidine (642.9 mg, 6 mmol) and tert.butyldimethylsilyltrifluoromethane sulfonate (1.0573g, 4 mmol) and the reaction mixture was stirred for 2hr. Water was added and extracted with ethylacetate. The organic layer was washed with water, brine, dried (Na₂SO₄) and solvent evaporated. The crude product obtained was dissolved in THF (20 ml), water (2 ml) and acetic acid (7 ml) were added and the mixture was stirred overnight at room temperature. Added water and extracted with ethylacetate. The organic layer was washed with water, brine, dried (Na₂SO₄) and solvent evaporated. Purification of the crude product by column chromatography over silica gel afforded the acids **36-39** as a mixture of diastereomers (590 mg, 78%).

Macrolactonization of the acids **36-39**:

To a solution of the mixture of the acids **36-39** (590 mg, 0.78 mmol) in THF (7 ml) at 0°C was added triethylamine (552 mg, 5.46 mmol) and 2,4,6-trichlorobenzoyl chloride (951 mg, 3.9 mmol). The mixture was stirred for 30 min and transferred via a cannula to a solution of DMAP (1.05 g, 8.58 mmol) in toluene (433 ml). The turbid solution obtained was stirred overnight and toluene was removed under reduced pressure. The residue obtained was purified by column chromatography over silica gel (5% ethylacetate in hexanes) to give the lactones **40-43**.

Lactone **40** (156 mg, 27%):

¹H NMR (400 MHz CDCl₃): δ 5.41 (dt, J = 9.2, 4.1 Hz, 1H), 5.35-5.25 (m, 1H), 5.13 (dt, J = 8.7, 2.5 Hz, 1H), 4.38 (dd, J = 7.0 Hz, 1H), 4.0 (dd, J = 5.0, 2.5 Hz, 1H), 2.97 (dq, J = 7.0 Hz, 1H), 2.52-2.32 (m, 3H), 2.26 (dd, J = 17.1, 2.4 Hz, 1H), 2.16 (s, 3H), 2.12-2.02 (m, 1H), 2.0-1.88 (m, 1H), 1.62-1.48 (m, 2H), 1.27 (s, 3H), 1.2-1.1 (m, 2H), 1.13 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 0.9-0.85 (m, 12H), 0.84 ((s, 9H), 0.09 (s, 3H), 0.06 (s, 6H), 0.00 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 219.2, 205.5, 170.9, 135.5, 123.5, 78.44, 74.7, 72.7, 53.9, 44.5, 40.8, 35.2, 32.9, 29.2, 28.5, 27.4, 26.8, 26.5, 26.3, 18.7, 18.6, 17.6, 16.9, 15.2, -3.6, -3.8, -4.0, -4.3.

Lactone **41** (98 mg, 17%):

^1H NMR (400 MHz CDCl_3): δ 5.6-5.5 (m, 1H), 5.25-5.15 (m, 1H), 5.07 (t, $J = 4.36$, 1H), 4.28 (dd, $J = 7.6$, 2.0 Hz, 1H), 3.81 (d, $J = 7.2$ Hz, 1H), 3.07 (dq, $J = 7.0$ Hz, 1H), 2.77 (ddd, $J = 14.7$, 9.6, 5.4 Hz, 1H), 2.62 (dd, $J = 17.6$, 1.9 Hz, 1H), 2.53 (dt, $J = 14.9$, 5.1 Hz, 1H), 2.45 (dd, $J = 17.6$, 7.9 Hz, 1H), 2.19 (s, 3H), 1.95-1.75 (m, 2H), 1.9-1.8 (m, 2H), 1.27 (s, 3H), 1.19-1.1 (m, 2H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.88-0.80 (m, 12H), 0.13 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (100 MHz CDCl_3): δ 218.8, 206.2, 171.6, 134.7, 123.0, 79.1, 76.3, 72.0, 54.2, 47.4, 40.1, 38.6, 34.5, 28.6, 27.6, 27.2, 26.9, 26.6, 26.5, 24.1, 19.1, 19.0, 18.0, 17.3, 13.8.

Lactone 42 (57 mg, 10 %):

^1H NMR (400 MHz CDCl_3): δ 5.54-5.45 (m, 1H), 5.28-5.2 (m, 1H), 5.07 (dd, $J = 7.3$, 3.4 Hz, 1H), 4.34 (dd, $J = 7.6$, 2.6, 1H), 3.87 (dd, $J = 5.4$, 2.5 Hz, 1H), 2.98 (dq, $J = 6.1$ Hz, 1H), 2.72-2.65 (m, 1H), 2.58-2.44 (m, 3H), 2.19 (s, 3H), 2.1-1.95 (m, 3H), 1.60-1.48 (m, 1H), 1.48-1.38 (m, 2H), 1.3-1.2 (m, 1H), 1.22 (s, 3H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.05 (s, 3H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H).

Lactone 43 (81 mg, 14 %):

^1H NMR (400 MHz CDCl_3): δ 5.61-5.51 (m, 1H), 5.36-5.25 (m, 2H), 4.51 (dd, $J = 4.4$, 3.0 Hz, 1H), 3.83 (d, $J = 9.2$ Hz, 1H), 3.11 (dq, $J = 9.0$, 6.6 Hz, 1H), 2.55-2.45 (m, 2H), 2.40-2.30 (m, 2H), 2.15 (s, 3H), 2.02-1.90 (m, 1H), 1.9-1.78 (m, 1H), 1.44-1.20 (m, 4H), 1.19 (s, 3H), 1.16 (s, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.89 (s, 9H), 0.88-0.80 (m, 12H), 0.01 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (100 MHz CDCl_3): δ 220.5, 206.0, 171.5, 134.9, 123.4, 78.0, 76.9, 71.6, 55.0, 46.6, 42.2, 37.8, 34.7, 29.4, 27.3, 27.1, 26.6, 26.4, 26.2, 26.0, 18.9, 18.7, 18.5, 16.7, 13.9, -2.9, -3.1, -3.8, -4.7

Conversion of the trisilyl ether 40 into lactone 45: Selective deprotection, Swern oxidation and the Wittig reaction sequence:

Selective deprotection:

A solution of the lactone **40** (73.8 mg, 0.1 mmol) in *tert*.BuOH (1 ml) and CH_2Cl_2 (0.25 ml) was added acetonitrile (3 ml) and hydrosilicic acid (14.4 mg, 0.1 ml) and the mixture

was stirred at room temperature for 36 h. Water was added and extracted with ethylacetate. The organic layer was washed with water, brine, dried (Na₂SO₄) and solvent evaporated. Purification of the crude product by silica gel chromatography (hexane: ethylacetate) yielded the corresponding pure alcohol (43mg, 69%).

¹H NMR (400 MHz CDCl₃): δ 5.4-5.3 (m, 2H), 4.83 (dt, J = 7.9, 2.0 Hz, 1H), 4.41 (d, J = 7.8 Hz, 1H), 4.12-4.06 (m, 1H), 3.88 (dq, J = 6.5 Hz, 1H), 2.48-2.39 (M, 1H), 2.36 (dd, J = 17.4, 8.5 Hz, 1H), 2.15-2.0 (m, 3H), 2.0-1.87 (m, 1H), 1.6-1.5 (m, 3H), 1.27 (s, 3H), 1.18 (d, J = 6.3 Hz, 3H), 1.15 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 0.89-0.86 (m, 12H), 0.85 (s, 9H), 0.11 (s, 3H), 0.07 (s, 6H), 0.01 (s, 3H).

Swern Oxidation:

DMSO (35.16 mg, 0.45 mmol) was added to a solution of oxalyl chloride (28.6 mg, 0.225 mmol) in CH₂Cl₂ (2 ml) at -78°C and stirred for 15 min. The alcohol obtained from the previous reaction (47 mg, 0.075 mmol) in CH₂Cl₂ was added slowly and stirring was continued for 2 h. Quenched with water, extracted with methylene chloride, washed with water, dried (Na₂SO₄) and solvent evaporated. Purification of the crude product on chromatography over silica gel (10% ethylacetate in hexanes) yielded the pure ketone **44** (42 mg, 90%).

¹H NMR (400 MHz CDCl₃): δ 5.41 (dt, J = 9.2, 4.1 Hz, 1H), 5.35-5.25 (m, 1H), 5.13 (dt, J = 8.7, 2.5 Hz, 1H), 4.38 (dd, J = 7.0 Hz, 1H), 4.0 (dd, J = 5.0, 2.5 Hz, 1H), 2.97 (dq, J = 7.0 Hz, 1H), 2.52-2.32 (m, 3H), 2.26 (dd, J = 17.1, 2.4 Hz, 1H), 2.16 (s, 3H), 2.12-2.02 (m, 1H), 2.0-1.88 (m, 1H), 1.62-1.48 (m, 2H), 1.27 (s, 3H), 1.2-1.1 (m, 2H), 1.13 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 0.9-0.85 (m, 12H), 0.84 ((s, 9H), 0.09 (s, 3H), 0.06 (s, 6H), 0.00 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 219.2, 205.5, 170.9, 135.5, 123.5, 78.44, 74.7, 72.7, 53.9, 44.5, 40.8, 35.2, 32.9, 29.2, 28.5, 27.4, 26.8, 26.5, 26.3, 18.7, 18.6, 17.6, 16.9, 15.2, -3.6, -3.8, -4.0, -4.3.

Horner-Emmons reaction:

n-Butyllithium (5.12 mg, 0.08 mmol) was added to a solution of the phosphonate **24** (20 mg, 0.08 mmol) in THF (1 ml) at -78°C and the mixture was stirred for 45 min at that temperature. The ketone **44** (25 mg, 0.04 mmol) in THF was added and the temperature was allowed to raise to room temperature. Stirred at room temperature

overnight, water was added and extracted with ethylacetate. The organic layer was washed with water, brine, dried (Na₂SO₄) and solvent evaporated to give the crude product. Purification by preparative TLC (5% EtOAc in hexanes) gave the starting ketone **44** (10 mg) and the product **45** (8.5 mg, 50%).

¹H NMR (400 MHz CDCl₃): δ 6.9 (s, 3H), 6.5 (s, 1H), 5.9-5.78 (m, 3H), 4.36 (dd, J = 8.2, 1.4 Hz, 1H), 4.08 (t, J = 3.3 Hz, 1H), 2.98 (dq, J = 7.0 Hz, 1H), 2.70 (s, 3H), 2.62-2.52 (m, 1H), 2.38 (dd, J = 17.2, 8.3 Hz, 1H), 1.68-1.5 (m, 3H), 1.31 (s, 3H), 1.19-1.09 (m, 2H), 1.14 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H), 0.92-0.85 (m, 12 H), 0.78 (s, 9H), 0.1-0.04 (m, 9H), -0.07 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 219.2, 170.5, 164.9, 152.9, 138.4, 134.3, 125.2, 120.0, 116.3, 78.2, 73.8, 73.1, 53.6, 44.3, 41.4, 40.7, 33.3, 32.6, 28.8, 27.5, 26.7, 26.5, 23.3, 19.6, 18.7, 18.6, 17.5, 16.4, 15.6, 14.7, -3.8, -3.9, -4.1, -4.3.

Conversion of the compound **41** in to the lactone **47**:

Selective deprotection of the silyl ether was carried out as described for **40** to give the corresponding alcohol in 75 % yield.

¹H NMR (400 MHz CDCl₃): δ 5.53 (dt, J = 9.0, 8.7 Hz, 1H), 5.42 (dt, J = 9.0, 8.8 Hz, 1H), 4.6 (dt, J = 7.0, 5.4 Hz, 1H), 4.30 (d, J = 7.0 Hz, 1H), 3.90 (dq, J = 6.1 Hz, 2H), 3.81 (d, J = 7.6 Hz, 1H), 3.08 (dq, J 6.7 Hz, 1H), 2.64 (ddd, J = 14.7, 8.6, 5.2 Hz, 1H), 2.46 (d, J = 18.0 Hz, 1H), 2.3 (dd, J = 17.8, 7.3 Hz, 2H), 1.95-1.7 (m, 3H), 1.37-1.25 (m, 1H), 1.29 (s, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.23-1.13 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 1.10 (s, 3H), 0.89 (s, 9H), 0.87-0.82 (m, 21H), 0.14 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 171.9, 133.6, 124.5, 78.7, 76.5, 71.3, 68.3, 54.3, 47.4, 39.9, 38.0, 34.4, 27.2, 26.9, 26.7, 26.7, 26.5, 24.3, 19.9, 19.0, 18.8, 18.5, 17.7, 13.4, -2.9, -3.4, -3.7, -4.3.

Swern oxidation of the alcohol obtained from the above reaction following the procedure described earlier resulted in the corresponding ketone in 92% yield.

¹H NMR (400 MHz CDCl₃): δ 5.6-5.5 (m, 1H), 5.25-5.15 (m, 1H), 5.07 (t, J = 4.36, 1H), 4.28 (dd, J = 7.6, 2.0 Hz, 1H), 3.81 (d, J = 7.2 Hz, 1H), 3.07 (dq, J = 7.0 Hz, 1H), 2.77 (ddd, J = 14.7, 9.6, 5.4 Hz, 1H), 2.62 (dd, J = 17.6, 1.9 Hz, 1H), 2.53 (dt, J = 14.9, 5.1 Hz, 1H), 2.45 (dd, J = 17.6, 7.9 Hz, 1H), 2.19 (s, 3H), 1.95-1.75 (m, 2H), 1.9-1.8 (m,

2H), 1.27 (s, 3H), 1.19-1.1 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 1.05 (s, 3H), 0.89 (s, 9H), 0.88-0.80 (m, 12H), 0.13 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 218.8, 206.2, 171.6, 134.7, 123.0, 79.1, 76.3, 72.0, 54.2, 47.4, 40.1, 38.6, 34.5, 28.6, 27.6, 27.2, 26.9, 26.6, 26.5, 24.1, 19.1, 19.0, 18.0, 17.3, 13.8.

Horner-Emmons reaction of the ketone obtained above following the procedure described for **44** yielded the lactone **47** in 52% yield.

¹H NMR (400 MHz CDCl₃): δ 6.96 (s, 1H), 6.55 (s, 1H), 5.58-5.48 (m, 1H), 5.38-5.29 (m, 1H), 5.29-5.22 (t, J = 4.4 Hz, 1H), 4.31 (dd, J = 7.0, 2.9 Hz, 1H), 3.83 (d, J = 7.0 Hz, 1H), 3.08 (dq, J = 7.0 Hz, 1H), 2.81-2.70 (m, 1H), 2.71 (s, 3H), 2.57 (dd, J = 17.8, 3.3 Hz, 1H), 2.41 (dd, J = 17.8, 7.0 Hz, 2H), 2.08 (s, 3H), 2.09-1.95 (m, 1H), 1.93-1.8 (m, 1H), 1.42-1.30 (m, 2H), 1.29 (s, 3H), 1.20-1.10 (m, 2H), 1.10 (d, J = 6.9 Hz, 3H), 1.06 (s, 3H), 0.92-0.8 (m, 21H), 0.14 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 219.0, 171.6, 153.0, 151.0, 136.9, 133.7, 124.0, 119.8, 116.4, 78.3, 76.2, 71.8, 54.1, 47.4, 40.1, 38.2, 34.3, 30.43, 27.1, 26.9, 26.7, 26.5, 24.2, 19.6, 19.2, 19.0, 18.8, 17.4, 16.2, 13.8, -2.9, -3.4, -3.6, -4.4.

Conversion of the compound **42** in to the lactone **48**:

Selective deprotection of the silyl ether was carried out as described for **40** to give the corresponding alcohol in 71 % yield.

¹H NMR (400 MHz CDCl₃): δ 5.5-5.35 (m, 2H), 4.77 (dt, J = 5.9, 4.8 Hz, 1H), 4.41 (dd, J = 8, 1.7 Hz, 1H), 4.97-3.88 (m, 2H), 2.88 (dq, J = 6.9 Hz, 1H), 2.5-2.43 (m, 2H), 2.36 (d, J = 8Hz, 1H), 2.30 (dd, 16.9, 1.9 Hz, 1H), 2.14-2.04 (m, 1H), 2.0-1.9 (m, 1H), 1.8-1.74 (m, 1H), 1.58-1.45 (m, 1H), 1.30-1.124 (m, 2H), 1.21 (d, J = 6.4 Hz, 3H), 1.19 (s, 3H), 1.3 (d, J = 7.0 Hz, 3H), 1.05 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 217.6, 171.8, 133.2, 125.5, 78.3, 76.4, 73.1, 69.2, 53.9, 41.0, 40.3, 31.9, 28.4, 27.4, 27.1, 26.5, 26.3, 23.0, 20.3, 19.5, 18.8, 18.7, 16.9, 14.4, -3.4, -3.6, -3.6, -4.1.

Swern oxidation of the alcohol obtained from the above reaction following the procedure described earlier resulted in the corresponding ketone in 85% yield.

¹H NMR (400 MHz CDCl₃): δ 5.54-5.45 (m, 1H), 5.28-5.2 (m, 1H), 5.07 (dd, J = 7.3, 3.4 Hz, 1H), 4.34 (dd, J = 7.6, 2.6, 1H), 3.87 (dd, J = 5.4, 2.5 Hz, 1H), 2.98 (dq, J = 6.1 Hz, 1H), 2.72-2.65 (m, 1H), 2.58-2.44 (m, 3H), 2.19 (s, 3H), 2.1-1.95 (m, 3H), 1.60-1.48 (m, 1H), 1.48-1.38 (m, 2H), 1.3-1.2 (m, 1H), 1.22 (s, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.05 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H).

Horner-Emmons reaction of the ketone obtained above following the procedure described for **44** yielded the lactone **48** in 48 % yield.

Conversion of the compound **43** in to the lactone **49**:

Selective deprotection of the silyl ether was carried out as described for **40** to give the corresponding alcohol in 63 % yield.

¹H NMR (400 MHz CDCl₃): δ 5.60-5.46 (m, 1H), 5.50-5.36 (m, 1H), 4.90-4.82 (m, 1H), 4.57 (dd, J = 5.8, 2.0 Hz, 1H), 3.90-3.80 (m, 2H), 3.09 (dq, J = 7.0 Hz, 1H), 2.48-2.35 (m, 1H), 2.28 (dd, J = 17.7, 6.2 Hz, 1H), 2.22-2.10 (m, 2H), 2.0-1.75 (m, 3H), 1.48-1.28 (m, 2H), 1.18 (s, 3H), 1.18 (d, J = 6.0 Hz, 3H), 1.14 (s, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.85-0.78 (m, 12H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

¹³C NMR (100 MHz CDCl₃) δ 219.7, 170.7, 132.9, 124.3, 76.7, 75.6, 70.7, 68.5, 53.8, 46.0, 41.1, 36.7, 33.2, 27.5, 25.9, 25.8, 25.7, 24.9, 18.5, 18.2, 17.8, 17.8, 15.9, 12.8, -3.8, -3.9, -4.5, -5.4.

Swern oxidation of the alcohol obtained from the above reaction following the procedure described earlier resulted in the corresponding ketone in 88% yield .

¹H NMR (400 MHz CDCl₃): δ 5.61-5.51 (m, 1H), 5.36-5.25 (m, 2H), 4.51 (dd, J = 4.4, 3.0 Hz, 1H), 3.83 (d, J = 9.2 Hz, 1H), 3.11 (dq, J = 9.0, 6.6 Hz, 1H), 2.55-2.45 (m, 2H), 2.40-2.30 (m, 2H), 2.15 (s, 3H), 2.02-1.90 (m, 1H), 1.9-1.78 (m, 1H), 1.44-1.20 (m, 4H), 1.19 (s, 3H), 1.16 (s, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88-0.80 (m, 12H), 0.01 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H).

¹³C NMR (100 MHz CDCl₃): δ 220.5, 206.0, 171.5, 134.9, 123.4, 78.0, 76.9, 71.6, 55.0, 46.6, 42.2, 37.8, 34.7, 29.4, 27.3, 27.1, 26.6, 26.4, 26.2, 26.0, 18.9, 18.7, 18.5, 16.7, 13.9, -2.9, -3.1, -3.8, -4.7

Horner-Emmons reaction of the ketone obtained above following the procedure described for **44** yielded the lactone **49** in 45 % yield.

^1H NMR (400 MHz CDCl_3): δ 6.9 (s, 1H), 6.4 (s, 1H), 5.58-5.48 (m, 1H), 5.46-5.42 (m, 1H), 5.42-5.33 (m, 1H), 4.55 (dd, $J = 6.0, 2.5$ Hz, 1H), 3.87 (d, $J = 9.0$ Hz, 1H), 3.13 (dq, $J = 8.9, 6.8$ Hz, 1H), 2.70 (s, 3H), 2.51 (dt, $J = 14.2, 8.1$ Hz, 1H), 2.38-2.32 (m, 1H), 2.30 (d, $J = 6.0$ Hz, 1H), 2.23 (dd, $J = 17.6, 2.5$ Hz, 1H), 2.07 (s, 3H), 2.07-1.95 (m, 1H), 1.46-1.3 (m, 3H), 1.2 (s, 3H), 1.16 (s, 3H), 1.11 (d, $J = 6.9$ Hz, 3H), 0.90 (s, 9H), 0.87 (d, $J = 6.7$ Hz, 3H), 0.83 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (100 MHz CDCl_3): δ 220.4, 171.1, 164.9, 153.7, 138.0, 133.6, 125.0, 119.3, 116.1, 77.29, 76.6, 71.6, 54.7, 46.8, 42.0, 37.8, 34.2, 32.0, 27.1, 26.6, 26.4, 26.4, 25.9, 19.6, 18.9, 18.6, 18.5, 16.8, 16.1, 13.7.

Preparation of **81**:

To a flame dried Mg in THF (5 ml) under argon a crystal of I_2 and TIPSBr, **80** (2.95g, 10.0 mmol) in THF (5 ml) was added slowly. After the completion of the addition it was refluxed for 30 min. Grignard reagent was then added to CuBr•DMS complex (2.055g, 10.0 mmol) in ether (15 ml) and DMS (10 ml) at -45°C . It was allowed to stir at -45°C for 2.5 h. To this propyne (400mg, 10 mmol) was added by condensing at -50°C with the help of cold finger. Then the reaction mixture was brought to -23°C and stirred at this temperature for 3h. Then the reaction mixture was cooled to -50°C and I_2 was added and slowly allowed the reaction mixture to bring to -15°C and stirred for 30 min and then quenched with NH_4Cl saturated solution. Extracted with ether (3 x 50 ml) and combined organic extracts were washed with water, brine dried over Na_2SO_4 . Evaporation of the solvent and purification by column chromatography over silica gel afforded the product **81** (0.582g, 30%).

^1H NMR (400 MHz in CDCl_3) δ 6.00 (s, 1H), 3.84 (t, $J = 12$ Hz, 2H), 2.38 (t, $J = 8.1$ Hz, 2H), 2.01 (s, 3H), 1.7 (m, 2H), 1.37 (m, 3H), 1.19 (d, $J = 4.8$ Hz, 18 H).

^{13}C NMR (100 MHz in CDCl_3) δ 145.1, 138.7, 112.8, 75.8, 71.3, 20.6, 17.7, -0.07

Preparation of **82**:

A solution of iodo compound **81** (1.905g, 5.0 mmol) in toluene (10 ml) at 0°C was treated with n-BuLi (320mg, 2.0 ml of 2.5 M solution in hexane) and stirred for 15 min,

followed by addition of dimethylaluminium chloride (462.5 mg, 4.9 ml of 1.0 M solution in hexane). The reaction mixture was stirred at 0°C for 45 min and epoxide (1.623g, 5.0 mmol) in toluene (5.0 ml) was added. The contents were stirred at room temperature for 5h. Quenched the reaction by addition of saturated Na₂SO₄ solution and extracted with ethylacetate. Organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent and purification by column chromatography over silica gel afforded the product **82** (2.46g, 85%).

¹H NMR (400 MHz in CDCl₃) δ 7.6 (m, 4H), 7.24 (m, 6H), 4.98 (t, J = 8.0 Hz, 1H), 3.7 (m, 1H), 3.57 (m, 3H), 1.9 (m, 2H), 1.59 (s, 3H), 1.49 (m, 2H), 1.2 (m, 3H), 1.01 (d, J = 8.0 Hz, 18H), 0.9 (s, 9H).

Preparation of **83**:

A mixture of **82** (2.46g, 4.23 mmol) and 0.01 N HCl (4.0 ml) in ethanol was stirred under reflux for 3h. The solvent was removed under reduced pressure and the residue was extracted into diethyl ether (2 x 25 ml) and washed successively with saturated solution of NaHCO₃, brine. Combined organic extracts were dried (Na₂SO₄). Evaporation furnished a colorless oil which was purified by flash column chromatography over silica gel to afford product **83** (1.71g, 95%).

¹H NMR (400 MHz in CDCl₃) δ 7.6 (d, J = 8.0 Hz, 4H), 7.33 (m, 6H), 5.02 (t, J = 8.6 Hz, 1H), 3.7 (m, 1H), 3.5 (m, 3H), 2.1 (m, 4H), 1.59 (s, 3H), 0.99 (brs, 12H).

Preparation of **84**:

p-Toluene sulfonyl chloride (0.835g, 4.39 mmol) was added in portionwise to a solution of **83** (1.71g, 3.99 mmol) in dichloromethane (10 ml), pyridine (0.5 ml) and DMAP(catalytic). Reaction mixture was stirred for 6h at room temperature and saturated NaHCO₃ was added. Extracted with EtOAc (2 x 20 ml) and combined organic layer was washed with 10% HCl, saturated NaHCO₃ and brine. Organic layer was dried over (Na₂SO₄). Evaporation of the organic solvent and purification of the crude product afforded **84** (2.12g, 92%).

¹H NMR (400 MHz in CDCl₃) δ 7.76 (d, J = 12 Hz, 2H), 7.58 (m, 4H), 7.3 (m, 6H), 7.24 (d, J = 10 Hz, 2H), 4.8 (t, J = 8.0 Hz, 1H), 3.89 (t, J = 14.0 Hz, 2H), 3.72 (m, 1H), 3.48 (m, 1H), 2.35 (s, 3H), 1.97 (m, 4H), 1.58 (m, 2H), 1.51 (s, 3H), 0.98 (s, 9H), 0.93 (d, J = 8.0 Hz, 3H).

Preparation of 85:

To a solution of **84** (2.12g, 3.66 mmol) in dichloromethane (20 ml) at 0°C, 2,6-lutidine (0.54 ml, 4.39 mmol) and tert. butyldimethyl trifluoromethane sulfonate (0.846 ml, 4.39 mmol) and stirred the contents for 2h. Diluted with CH₂Cl₂ (20 ml) and was washed with 10% aqueous HCl (2 x 10 ml), followed by water, brine. Organic layer was dried over (Na₂SO₄), evaporation of the organic solvent and purification by flash column chromatography over silica gel yielded **85** (2.41g, 96%).

¹H NMR (400 MHz in CDCl₃) δ 7.75 (d, J = 12.0 Hz, 2H), 7.72 (m, 4H), 7.33 (m, 10H), 4.97 (t, J = 8.0 Hz, 1H), 3.9 (t, J = 8.2 Hz, 2H), 3.66 (m, 1H), 3.56 (m, 1H), 2.39 (s, 3H), 2.0-1.9 (m, 4H), 1.53 (s, 3H), 1.22 (m, 2H), 1.0 (s, 9H), 0.82 (brs, 12 H), 0.00 (s, 6H).

Preparation of 86:

A mixture of **85** (2.41g, 3.47 mmol) and NaI (0.624g, 4.16 mmol) in acetone was refluxed for 3h. Solvent was removed under reduced pressure and resulting residue was purified by column chromatography over silica gel to furnish **86** (1.94g, 88%).

¹H NMR (400 MHz in CDCl₃) δ 7.64 (m, 4H), 7.37-7.23 (m, 6H), 5.08 (t, J = 12.0 Hz, 1H), 3.75 (m, 1H), 3.58 (m, 1H), 3.06 (t, J = 8.0 Hz, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.7 (m, 2H), 1.59 (s, 3H), 1.03 (s, 9H), 0.89 (s, 9H), 0.019 (s, 3H), 0.00 (s, 3H).

¹³C NMR (100 MHz in CDCl₃) δ 145.1, 138.7, 121.0, 112.8, 75.8, 75.8, 71.3, 38.1, 36.8, 32.3, 31.0, 26.1, 25.9, 23.9, 20.6, 18.4, 17.7.

Preparation of 87:

To a solution of **18** (0.542g, 2.0 mmol) in THF (10 ml) n-BuLi (0.8 ml, 2.5 M solution in hexane) was added at -78°C over a period of 1h and the reaction mixture was stirred for 1h. To this HMPA (0.35 ml) and iodo compound **86** (1.27g, 2.0 mmol) in THF (5.0 ml)

were added. Slowly raised the reaction mixture to -30°C and stirred for 1h. Saturated NH₄Cl was added at 25°C and extracted with EtOAc (2 x 25 ml). Combined organic extracts were washed with water, brine and dried over (Na₂SO₄), evaporation of the organic solvent and purification by flash column chromatography over silica gel yielded **87** (1.01g, 65%).

¹H NMR (400 MHz in CDCl₃) δ 7.67 (d, J = 6.0 Hz, 4H), 7.37 (m, 6H), 5.08 (t, J = 7.2 Hz, 1H), 4.3 (d, J = 8.0 Hz, 1H), 3.65 (m, 1H), 3.48 (m, 1H), 3.2 (m, 2H), 2.9 (m, 1H), 2.1 (m, 2H), 1.8 (m, 10 H), 1.65 (s, 3H), 1.28 (m, 2H), 1.01 (brs, 13H), 1.07 (d, 3H), 0.99 (m, 15H), 0.06 (s, 6H).

¹³C NMR (100 MHz in CDCl₃) δ 190.8, 136.3, 136.0, 134.4, 129.9, 129.85, 127.8, 122.8, 77.86, 77.5, 77.2, 73.1, 66.2, 59.5, 57.4, 48.4, 44.9, 36.0, 28.8, 27.5, 26.6, 26.3, 23.7, 20.8, 19.7, 19.66, 18.5, 15.7, -3.8, -3.9

Preparation of **88**:

A solution of **87** (350 mg, 0.45 mmol) in ether was cooled to -78°C and was added LAH (0.5 ml, 1.0 M solution in diethyl ether) . Reaction mixture was slowly brought to room temperature over a period of 1h and saturated Na₂SO₄ was added. Reaction mixture was filtered and washed with water, brine and dried over (Na₂SO₄). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **88** (200 mg, 88%).

¹H NMR (400 MHz in CDCl₃) δ 7.67 (m, 4H), 7.37 (m, 6H), 5.09 (t, J = 7.8 Hz, 1H), 3.75 (m, 1H), 3.63 (m, 3H), 2.05-1.83 (m, 5H), 1.56 (s, 3H), 1.21 (m, 2H), 1.1 (d, J = 6.0 Hz, 3H), 1.05 (s, 9H), 0.98 (d, J = 8.0 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H),

Preparation of **21**:

Alcohol **88** (200mg) was dissolved in dichloromethane (10 ml). DMSO (1.0 ml), Et₃N (2.0 ml) and SO₃•py complex (300mg, 2.0 mmol) were added at 25 °C, and the resulting mixture was stirred for 30 min. Saturated aqueous NH₄Cl solution (5.0 ml) and ether (20 ml) were added sequentially. The organic phase was washed with brine, dried over (Na₂SO₄). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **21** (120mg).

Preparation of 90:

To a mixture of CuBr•DMS (4.1g, 20mmol), ether (25ml) and dimehtyl sulfide (20 ml), 0.5M solution of butenyl magnesium bromide (3.8g,40mmol) in ether was added over a period of 10min at -45°C. Reaction was stirred at this temperature for 2.5h and propyne (1.1 ml, 20m. mol) was added. This reaction mixture was stirred at -25°C for 3h and cooled to -78°C. To this 1-lithio pentyne (prepared from 20 mmol pentyne, 20 mmol n-BuLi and 20 mmol HMPA) in ether (20 ml) was added and stirred at -78°C for 1h. To this epoxide (7.0g, 20 mmol) was added and the reaction mixture was stirred at -78°C for 3h and at -25°C for 24h. Aqueous NH₄Cl was added and extracted with ether (2 x 100ml). Combined organic layer was washed with water, brine and dried (Na₂SO₄). Evaporation of organic solvent and purification by flash column chromatography gave the product **90** (3.03g, 55%).

¹H NMR (400 MHz in CDCl₃) δ 7.6 (d, J = 8.0 Hz, 4H), 7.31 (m, 6 H), 5.6-5.48 (m, 1H), 4.98 (t, J = 8.2 Hz, 1H), 4.85 (dd, J = 14.0, 12.0 Hz, 2H), 3.75 (m, 1H), 3.5 (m, 1H), 1.98-1.97 (m, 6H), 1.58 (s, 3H), 0.99 (s, 9H), 0.95 (d, J = 8.8 Hz, 3H).

Preparation of 92:

To a solution of **90** (3.03g, 7.03 mmol) in dichloromethane (20 ml), 2,6-lutidine (1.0 ml, 8 mmol) and TBDMSOTf (1.6g, 8 mmol) and stirred at 0°C for 2h. Diluted with CH₂Cl₂ (20 ml) and was washed successively with 10% aqueous HCl, water (20 ml) and brine. The organic layer was dried (Na₂SO₄). Evaporation of organic solvent and purification by flash column chromatography gave the product **92** (3.44g, 96%).

¹H NMR (400 MHz in CDCl₃) δ 7.63 (m, 4H), 7.32 (m, 6H), 5.7 (m, 1H), 5.02 (t, J = 7.2 Hz, 1H), 4.85 (dd, J = 14.0, 8.0 Hz, 2H), 2.18-1.88 (m, 6H), 1.58 (s, 3H), 1.0 (s, 9H), 0.91 (d, J = 8.0 Hz, 3H), 0.82 (s, 9H), -0.01 (s, 3H), -0.01 (s, 3H).

To a stirred solution of **92** (2.56g) and tert. BuOH and water (1:1), AD-mix- α was added. Reaction mixture was stirred at room temperature for 10h. The volume of the reaction mixture was reduced to 1/4 by evaporating under vacuum. Diluted with ethylacetate (25 ml) and washed with water, brine, dried (Na₂SO₄). Evaporation of organic solvent and

purification by flash column chromatography gave the corresponding diol (2.268g, 75%).

^1H NMR (400 MHz in CDCl_3) δ 7.65 (m, 4H), 7.38-7.22 (m, 6H), 5.08 (t, $J = 14$, 8.2Hz, 1H), 3.78 (m, 1H), 3.52-3.6 (m, 3H), 3.35 (m, 1H), 2.04-1.99 (m, 4H), 1.6 (s, 3H), 1.23 (m, 2H), 1.02 (s, 9H), 0.93 (d, $J = 8.0$ Hz, 3H), 0.84 (s, 9H), 0.022 (s, 3H), 0.00 (s, 3H).

Preparation of 94:

To a solution of diol obtained in the above step (2.04g, 3.75 mmol) in 1: 1 mixture of THF/ H_2O (20 ml) sodiumperiodate was added and the mixture was stirred at 25°C for 30 min. Reaction mixture was diluted with ether and washed with water, brine, dried over (Na_2SO_4). Organic solvent was removed and the residue was dissolved in methanol (10 ml) and cooled to 0°C . To this sodium borohydride (144mg, 3.8 mmol) was added and stirred at 0°C for 1h. Water was added and extracted with ether (2 x 25 ml). Combined organic layer was washed with water, brine, dried (Na_2SO_4). Evaporation of organic solvent and purification by flash column chromatography gave the primary alcohol **94** (1.5g, 80%).

^1H NMR (400 MHz in CDCl_3) δ 7.64 (m, 4H), 7.3 (m, 6H), 5.08 (t, $J = 8.2$ Hz, 1H), 3.75 (m, 1H), 3.58 (m, 1H), 3.52 (t, $J = 14.0$ Hz, 2H), 2.09-1.95 (m, 4H), 1.61 (s, 3H), 1.19 (s, 9H), 1.01 (d, $J = 8.0$ Hz, 3H), 0.84 (s, 9H), 0.021 (s, 3H), 0.00 (s, 3H).

Preparation of 115:

Ozone was bubbled through a solution of citronellene, **114** (10g, 72.46 mmol) in dichloromethane (500ml) at -78°C . Reaction progress was monitored by the concentration of citronellene. After 6h argon was bubbled through the reaction mixture to remove the excess ozone. MeOH (10ml) was added followed by the addition of sodium borohydride (5.7g, 155mmol) and the reaction mixture was slowly brought to room temperature and stirred for 2h. Water was added to the reaction mixture and extracted with ether (2x 500ml), washed with water, brine, and dried (Na_2SO_4). Organic solvent was removed at room temperature and the residue was purified by flash column chromatography (pentane and ether) to afford the alcohol **115** (6.7g, 81%).

^1H NMR (400 MHz in CDCl_3) δ 5.7 (dq, $J = 4.1$, 6Hz, 1H); 4.96 (dd, $J = 6.2$, 8 Hz, 2H), 3.65 (t, $J = 6.1$ Hz, 2H), 2.15 (m, 1H), 1.58 (m, 2H), 1.4 (brs, 1H), 1.3 (d, $J = 6$ Hz, 3H).
 ^{13}C NMR (100 MHz in CDCl_3) δ 148, 113.4, 37.7, 35, 34.2, 31.1, 20.4

Preparation of 116:

p-Toluenesulfonyl chloride (7.7g, 40mmol) was added to a stirred and ice cold solution of 4(S)- 4-methyl -5-ene-1-ol (**115**) in dry pyridine (25ml). The mixture was stirred for 1.5h at 0-5°C. Then it was poured into ice cooled water and extracted with ether. The ether solution was washed with water, CuSO_4 aq, NaHCO_3 aq, and brine. Dried(Na_2SO_4) and the solvent was removed to give 8.2g of crude tosylate. The crude product was dissolved in acetone (100ml), LiBr (7.2g) was added to the solution and the mixture was stirred and heated at reflux for 1.5h and then stirred at room temperature for 10h. It was poured into icecooled water and extracted with ether (2x100). The ether solution was washed with water, NaHCO_3 aq, brine, and dried(Na_2SO_4) and solvent was removed at room temperature. The residue was distilled to give bromide **116** (4.46g, 75.6%).

^1H NMR (400 MHz in CDCl_3) δ 5.6 (m, 1H), 4.9 (dd, $J = 6$, 8 Hz, 2H), 3.32 (t, $J = 7$ Hz, 2H), 2.07 (m, 1H), 1.77 (m, 2H), 1.38 (m, 2H), 0.94 (d, $J = 7$ Hz).

^{13}C NMR (100 MHz in CDCl_3) δ 144.3, 113.5, 37.6, 35.41, 34.25, 31.01, 20.66

Preparation of 118:

To a mixture of $\text{CuBr} \cdot \text{DMS}$ complex (4.1g, 20mmol), ether (25ml) and dimehtyl sulfide (20 ml) S-4-methyl -hexyl - 5- enyl magnesium bromide (3.8g, 40mmol) in ether was added over a period of 5 min at -45°C. Reaction was stirred at this temperature for 2.5h and propyne (2.5ml, 40 mmol) was added. This reaction mixture was stirred at -25°C for 3h and cooled to -78°C. To this 1-lithio pentyne (prepared from 40 mmol pentyne, 40 mmol of n-BuLi and 40 mmol HMPA) in ether (20 ml) was added and stirred at -78°C for 1h. To this epoxide (4.04g, 40mmol) was added and the reaction mixture was stirred at -78°C for 3h and at -25°C for 24h. NH_4Cl aq was added and extracted with ether (2 x 100ml). Combined organic layer was washed with water, brine and dried

(Na₂SO₄). Evaporation of organic solvent and purification by flash column chromatography gave the product **118** (4.51g, 65%).

¹H NMR (400 MHz in CDCl₃) δ 5.6 (m, 1), 5.16 (dd, J = 6, 6.1 Hz, 2H), 4.9 (t, J = 8 Hz, 1H), 3.72 (m, 1H), 3.5 (m, 1H), 2.07 (m, 4H), 1.98 (m, 1H), 1.6 (s, 3H), 1.2 (m, 2H), 1.15 (m, 2H), 1.04 (d, J = 7Hz, 3H), 0.91 (d, J = 7.2Hz, 3H), 0.82 (s, 9H), 0.006 (s, 6H).

¹³C NMR (100 MHz in CDCl₃) δ 157.5, 148.3, 145, 144.1, 135.1, 122, 77.6, 73.9, 70.1, 55.14, 54.26, 45.64, 17.48, -0.02, -0.01

Preparation of **120**:

To a suspension of NaH (240mg, 5mmol) in DMF (5ml), compd **118** (1.6g, 5 mmol) in DMF (10ml) was added and stirred at room temperature for 30 min. Then p-methoxybenzyl bromide was added and stirred at room temperature for 3h. Water was added slowly and extracted with ethylacetate (2x 25ml). Combined organic layer was washed with water, NaCl aq and dried (Na₂SO₄). Evaporation of solvent and purification by column chromatography gave the product **120** (1.84g, 81%).

¹H NMR (400 MHz in CDCl₃) δ 7.21 (d, J = 8Hz, 2H); 6.82 (d, J = 8.1 Hz, 2H) 5.6 (m, 1H) 5.17 (t, J = 6.1Hz, 1H), 4.85 (m, 2H), 4.5 (m, 2H), 3.75 (m, 4H), 3.2 (m, 1H), 2.12 (m, 1H), 2.1 (m, 4H), 1.62 (s, 3H), 1.19 (m, 2H), 1.123 (m, 2H), 1.08 (d, J = 8Hz, 2H) 0.93 (d, J = 7.8 Hz, 2H), 0.84 (s, 9H), 0.007 (s, 3H), 0.00 (s, 3H).

¹³C NMR (100 MHz in CDCl₃) δ 164.1, 161.41, 157.15, 148.3, 145, 144.51, 135.1, 122, 77.6, 73.9, 70.1, 55.14, 54.26, 45.64, 17.48, -0.028, -0.019

A mixture of water (5ml), t-butanol (5ml) and compd **120** (1.8g, 4mmol) was added AD-mix-α 6g) at room temperature. Reaction mixture was stirred at room temperature for 12h. The volume of the reaction mixture was then reduced to half and extracted with ethyl acetate (2x 25ml). The combined organic layer was washed with water, NaCl aq and dried (Na₂SO₄). Evaporation of the solvent and purification by flash column chromatography afforded corresponding diol, 1.542g (78%).

¹H NMR (400 MHz in CDCl₃) δ 7.21 (d, J = 8Hz, 2H); 6.82 (d, J = 7.8 Hz); 5.17 (t, J= 6.1 Hz, 1H); 4.48 (dd, J = 8, 14 Hz; 2H); 3.75 (s, 3H); 3.7 (m, 1H), 3.48 (m, 1H), 3.39 (m, 2H), 3.2 (m, 1H); 2.11 (m, 1H), 1.94 (m, 4H), 1.61 (s, 3H), 1.48-1.2 (m, 4H), 1.06 (d, J = 6.2 Hz, 3H), 0.84 (s, 9H); 0.825 (d, , J= 6 Hz, 3H), 0.0085 (s, 3H), -0.0119 (s, 3H).

Preparation of 122:

To a solution of diol (988 mg, 2 mmol) in THF(5 ml) and water (5 ml) powdered sodiumperiodate was added at room temperature. It was allowed to stir for 1h and diluted with ether and organic layer was separated. Organic layer was washed with water, NaCl aq and dried (Na₂SO₄). Evaporation of the solvent and purification by flash chromatography afforded aldehyde (0.728 g, 85%).

¹H NMR (400 MHz in CDCl₃) δ 9.1 (d, J = 6Hz, 1H,); 7.21 (d, J = 8Hz, 2H,)); 6.82 (d, J = 7.8 Hz,); 5.17 (t, J = 6.1 Hz, 1H); 4.48 (dd,J = 8, 14 Hz; 2H,); 3.75 (s, 3H); 3.7 (m, 1H-); 3.2 (m, 1H); 2.11 (m, 1H), 1.94 (m, 4H), 1.61 (s, 3H,) 1.48-1.2 (m, 4H), 1.06 (d, J = 6.2 Hz, 3H), 0.84 (s, 9H), 0.825 (d, , J =- 6 Hz, 3H,) 0.0085 (s, 3H,) -0.0119 (s, 3H)

p- Toluene sulfonylchloride (36g, 0.24 mol) was added to a stirred and ice cooled solution of alcohol (20g, 0.2 mol) in dry pyridine (150 ml). The mixture was stirred for 1.5 h at 0 - 5 °C. Then it was poured into icewater and extracted with ether (2 x 100ml). Combined organic layer was washed with water, CuSO₄ aq, NaHCO₃ aq,NaCl aq and dried (Na₂SO₄). Evaporation of the organic solvent gave 48g of crude product.

¹H NMR (400 MHz in CDCl₃) δ 7.7 (dd, j = 8.12 Hz, 2H); 7.33 (d, J = 8.2 Hz); 4.68 (s, 1H); 4.58 (s, 1H), 4.02 (t, J = 6.4,6.43 Hz; 2H); 2.43 (s, 3H,); 2.01 (t, j = 7.4 Hz, 2H), 1.75 (t, J = 8 Hz, 14 Hz; 2H), 1.64 (s, 3H)

Preparation of 123:

Tosylate (48g, 0.188 mol) was dissolved in acetone (500 ml) and solid LiBr (19. 5 g, 0.226 mol) was added. The mixture was heated under reflux for 1.5 h and then stirred for 10 h. It was poured into ice water and extracted with ether (2x 250 ml). The

combined organic layer was washed with water, NaHCO₃ aq, NaCl aq and dried (Na₂SO₄). The organic solvent was removed at room temperature and the residue was distilled to give **123** (22. 84g, 76%).

¹H NMR (CDCl₃, 400 Mhz) δ 4.76 (s, 1H); 4.72 (s, 1H,); 3.4 (t, J = 6.7, 6.5 Hz; 2H); 2.16 (t, j = 7, 7.6 Hz; 2H), 2.01 (m, 1H); 1.7 (s, 3H).

¹³C NMR (CDCl₃ 400M Hz).

144.31, 111.39, 36.439, 33.65, 30, 29.9, 22.68.

Preparation of **124**:

To a mixture of CuBr•DMS complex (4.1g, 20 mmol), ether (25 ml), dimethylsulfide (20 ml) at -45°C was added a 0.46 M solution of grignard (43.0 ml, 20.0 mmol) in ether over a period of 10 min. After 2h, propyne (1.1ml, 20.0 mmol) which has been condensed by the cold finger at -45°C was added. The mixture was stirred at -23°C for 2.5 h and the resulting green solution was cooled to -78°C. A solution of 1-lithiopentyn [prepared from 20.0 mmol of pentyne and 20.0 mmol of n-BuLi in ether (20 ml)] and HMPA was transferred to the green solution. After 1h, epoxide (4.16g, 20.0 mmol) in ether (10 ml) was added over a 5 min period. The resulting mixture was stirred at -78°C for 3h and at -25°C for 24h. Quenched the reaction at 0°C by addition of saturated NH₄Cl solution (10 ml), adjusted the PH 8.0 with aqueous ammonia solution and partitioned between water and ether. The crude product was purified by flash column chromatography to yield (4.7g, 72%).

¹H NMR (400 MHz in CDCl₃) δ 5.16 (t, J = 14.0 Hz, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 3.78 (m, 1H), 3.48 (m, 1H), 2.07 (t, J = 10 Hz, 2H), 1.94 (m, 4H), 1.65 (s, 3H), 1.48 (m, 2H), 1.03 (d, J = 8.0 Hz, 3H), 0.82 (s, 9H), 0.006 (s, 3H), 0.00 (s, 3H).

Preparation of **125**:

To a solution of **124** (3.26g, 10.0 mmol) in dichloromethane (10 ml), 2,6-lutidine (1.28 ml) and TMSOTf (2.23 ml, 10.0 mmol) were added at 0°C. Reaction mixture was stirred at 0°C for 1h and aqueous NaHCO₃ solution was added. Extracted with ether (2 x 50 ml). Combined organic layer was washed with water, brine and dried over (Na₂SO₄).

Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **125** (3.78g, 95%).

^1H NMR (400 MHz in CDCl_3) δ 5.16 (t, J = 8.0 Hz, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 3.78 (m, 1H), 3.45 (m, 1H), 1.91 (m, 2H), 1.8 (m, 4H), 1.41 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H), 0.79 (s, 9H), -0.02 (s, 3H), -0.047(s, 3H).

Preparation of 126:

To a stirred solution of **125** (3.18g, 8.0 mmol) in THF (10 ml) at 25°C, $(\text{ipc})_2\text{BH}$ (2.28g, 8.0 mmol) in THF was added. Reaction mixture was stirred at 25°C for 1h and quenched with NaOH and H_2O_2 (10.0 mmol each). Extracted with ether and washed with water, brine, dried over (Na_2SO_4). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **126** (2.8g, 85%).

^1H NMR (400 MHz in CDCl_3) δ 5.11 (t, J = 8.2 Hz, 1H), 3.75 (m, 1H), 3.45 (m, 1H), 3.4 (m, 2H), 2.12 (m, 2H), 1.9 (m, 4H), 1.59 (s, 3H), 1.43 (m, 1H), 1.41 (m, 1H), 1.01 (d, J = 8.4 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.79 (s, 9H), -0.015 (s, 3H), -0.046 (s, 3H).

Preparation of 100:

To a solution of (2.08g, 5.0 mmol) in CH_2Cl_2 (20 ml) and DMSO (2 ml) at 0°C, was added triethylamine ((2.0 ml) and $\text{SO}_3\cdot\text{py}$ complex (1.59g, 10.0 mmol) and the resulting mixture was stirred at 0°C for 90 min. Reaction mixture was quenched by addition of aqueous NH_4Cl (2.0 ml) and extracted with diethyl ether (2 x 25 ml). Combined organic extracts was washed with water, brine dried over (Na_2SO_4). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave aldehyde (1.73g, 84%).

^1H NMR (400 MHz in CDCl_3) δ 9.52 (s, 1H), 5.1 (t, J = 6.5 Hz, 1H), 3.5 (m, 1H), 3.29 (dt, J = 5.2, 4.0 Hz, 1H), 2.21 (dd, J = 4.8, 3.6 Hz, 2H), 2.08 (m, 1H), 1.94 (m, 2H), 1.61 (s, 3H), 1.32 (m, 2H), 1.01 (d, 6H), 0.79 (s, 9H), 0.065 (s, 3H), -0.025 (s, 3H).

Preparation of 5c:

To a suspension of NaH (0. 96g, 20mmol) in THF (20ml), cooled to 0°C, was added epoxy alcohol (1.76g, 20 mmol) in THF (10 ml). It was allowed to stir at 0°C for 30 min

and p- methoxy benzylbromide was added slowly. Reaction was quenched with cooled water and extracted with ethyl acetate (2x 25 ml). Combined organic layer was washed with water, NaCl aq and dried (Na₂SO₄).Evaporation of the organic solvent and purification by column chromatography afforded **5c** 3.5g (87%).

¹H NMR (CDCl₃,400 M Hz). 7.25 (d, J = 8Hz, 2H) 6.87 (d, J = 8.1 Hz, 2H), 4.55 (dd, j = 12, 8 Hz; 2H),3.79 (s, 3H,); 3.4 - 3. 38 (dq,J = 8, 5.6 Hz, 1H,); 2.92 (dq, J = 1.4, 0.8Hz, 2.78 (dd, J = 4.7, 3.9 Hz, 1H); 2.68 (dd, J = 2.3, 2.58 Hz, 1H); 1.28 (d, J = 6.3 Hz, 3H)

¹³C NMR (CDCl₃ 400M Hz).

159.18, 130.52, 129.06, 113.77, 73.9, 70.94, 55.15, 54.26, 45.64, 17.48

Preparation of 130:

To a mixture of CuBr• DMS complex (4.1g, 20 mmol), ether (25 ml), and dimethyl sulfide (20 ml) at -45°C was added a 0.46 M solution of grignard reagent (43 ml, 20 mmol) in ether over a period of 5 min. After 2h, propyne (1.1 ml, 20 mmol) which had been condensed by cooled finger , at -45°C was added. The reaction mixture was stirred at -23°C for 2.5 h and the resulting dark green solution was cooled to -78°C. A solution of 1- lithiopentyne (prepared from pentyne(20mmol) and n- BuLi (20 mmol) in ether (20 ml)and HMPA (20 mmol) was transfereed to the green solution. Aftr 1h epoxide (4.16g, 20 mmol) in ether (10 ml) was added over a 5min period. the resultin mixture was stirred at -78°C for 3h and then at -25°C for 24 h, quenched at 0°C by addition of NH₄Cl aq (pH adjusted to 8 by NH₄OH) and partitioned between water and ether.The crude product was purified by flash column chromatography to yield **130** 4.7g(72%) product.

¹H NMR (CDCl₃,400 M Hz δ 7.26 (d, J = 7.5 Hz, 2H)), 6.88 (d, 2H, J = 8.1Hz, 2H), 5.17 (t, J = 8.2 Hz, 1H), 4.7 (s, 1H), 4.67 (s, 1H) 4.45 (dd, J = 12, 8 Hz; 2H), 3.8 (s, 3H,), 3.71 (m, 1H, -), 3.5 (m, 1H), 2.18 (m, 2H), 2.01 (m, 4H), 1.71 (s, 6H), 1.26 (m, 2H); 1,17 (d, J = 6.19, 3H).

¹³C NMR (CDCl₃ 400M Hz).

100.8, 95.4, 88.4, 79.9, 71.93, 65.48, 61.76, 31.2, 30.96, 27.53, 24.79, 10.57.

Preparation of 129:

To a solution of alcohol (4.7g, 14.1 mmol) in dichloromethane (25 ml) was added 2,6- lutidine (2ml, 16 mmol) and t-Butyl trifluoromethanesulfonate (3.2g, 16 mmol) and stirred at 0°C for 2h. Diluted with dichloromethane (25 ml) and washed with 10% aq Hydrochloric acid followed by water and NaCl aq and dried (Na₂SO₄). Organic solvent was evaporated and the resulting crude product was purified by flash column chromatography to afford **129** (5.9g ,95%). ¹H NMR (CDCl₃, 400 M Hz) δ 7.25 (d, J = 6.8 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 5.17 (t, J = 6.8 Hz, 1H), 4.7 (s, 1H), 4.67 (s, 1H), 4.48 (dd, J = 8, 6.5 Hz; 2H), 3.8 (s, 3H), 3.71 (m, 1H), 3.5 (m, 1H), 2.18 (m, 2H), 2.03 (m, 4H), 1.72 (s, 3H), 1.71 (s, 3H), 1.52 (m, 2H), 1.15 (d, J = 8 Hz, 3H), 0.93 (s, 9H), 0.0064 (s, 6H).

¹³C NMR (CDCl₃ 400M Hz).

146.26, 136.92, 131.642, 129.52, 122.22, 114.06, 110.2, 110, 75.746, 77.11, 71, 55.64, 38.170, 32.62, 32, 26.35, 23.89, 22.817, 18.59, 15.525.

Preparation of 130:

To a mixture of compound **129** (4.46 g, 10 mmol), dichloromethane (40 ml) and water (8 ml), was added DDQ (2.27 g, 10 mmol). Reaction mixture was stirred at 25°C for 30 min and the precipitate was filtered .The filtrate was washed NaHCO₃ aq, NaCl aq and dried (Na₂SO₄). Evaporation of the organic solvent and purification by column chromatography gave **130** (2.8 g , 88%).

¹H NMR (CDCl₃, 400 M Hz) δ 5.17 (t, J = 6.8 Hz, 1H); 4.7 (s, 1H, -C(CH₃)=CH₂), 4.67 (s, 1H, -), 3.8 (m, 1H), 3.6 (m, 1H), 2.15 (m, 2H), 2.04 - 1.9 (m, 4H), 1.71 (s, 3H), 1.69 (s, 3H), 1.51 (m, 2H), 1.1 (d, 3H, J = 7 Hz), 0.89 (s, 9H), 0.06 (s, 6H).

¹³C NMR (CDCl₃ 400M Hz).

146.15, 137.44, 121.81, 110.266, 77.727, 77.409, 77.09, 70.715, 38.1, 31.96, 30.7, 26.3, 23.8, 22.7, 18.4, 17.562, -0.06,

Preparation of 131:

Alcohol **130** (2.8g, 8.5 mmol) was dissolved in dichloromethane (45 ml), DMSO (24 ml), Et₃N (4.2 ml, 42 mmol), and SO₃•Py (2.7 g, 17 mmol) was added at 0°C and the resulting mixture was stirred at room temperature for 6h. NH₄Cl aq and ether were added sequentially. The organic layer was washed with water , NaCl aq and dried (Na₂SO₄) and the solvent was evaporated under reduced pressure. Purified by flash column chromatography furnished ketone **131** (1.59 g , 58%).

¹H NMR (CDCl₃, 400 M Hz) δ 5.17 (t, J = 7.2 Hz, 1H), 4.7 (s, 1H), 4.66 (s, 1H), 3.97 (t, J = 6.8 Hz, 1H), 2.25 (m, 2H), 2.14 (s, 3H), 1.7 (s, 3H), 1.68 (s, 3H), 1.4 (m, 2H), 0.94 (s, 9H), 0.04 (s, 6H)

¹³C NMR (CDCl₃ 400M Hz).

212.3, 146.1, 138.6, 119.7, 79.5, 77.7, 77.4, 77.0, 38.03, 33.74, 31.9, 26.6, 26.1, 25.7, 23.84, 22.77, 18.5.

Preparation of **132**:

Phosponate **24** (1.8 g, 7.6 mmol) was dissolved in dimethoxy ethane (20 ml) and the solution was cooled to -78°C. n-BuLi 3.04 ml, 2.5 M in hexane) was slowly added and the resulting mixture was stirred for 45 min before ketone (1.58 g, 4.8 mmol) in dimethoxyethane (10 ml) was added at the same temperature. Stirring was continued for another 10 h at room temperature and then the reaction mixture was quenched with NH₄Cl aq (25 ml) . Ethylacetate was added and the organic phase was separated and washed with water, NaCl aq and dried (Na₂SO₄) . Evaporation of the organic solvent and purification by flash column chromatography afforded compound **132** 1.58 g (75%).

¹H NMR (CDCl₃, 400 M Hz) δ 6.9 (s, 1H), 6.64 (s, 1H); 5.17 (t, J = 6.4 Hz, 1H), 4.66 (s, 1H), 4.64 (s, 1H), 4.15 (t, J = 6.2, 8 Hz, 1H), 2.7 (s, 3H), 2.2 (m, 2H), 2.0- 1.99 (m, 4H); 1.7 (s, 3H) ; 1.67 (s, 3H); 0.88 (s, 9H) 0.047 (s, 3H); 0.0032 (s, 6H).

¹³C NMR (CDCl₃ 400M Hz).

153, 146.2, 142.9, 137, 122.1, 119, 115.3, 110.1, 79.4, 77.7, 77.1, 38.1, 35.7, 32, 26.4, 26, 26.24, 23.8, 22.8, 19.5, 18.63, 14.32.

Preparation of 133:

To a solution of compound **132** (419 mg, 1 mmol) in THF (2 ml), (ipc)₂BH (286 mg, 1 mmol) in THF (2 ml) was added and the reaction was stirred for 1h at 25°C. Distilled water and Sodiumperborate (160 mg, 1.1 mmol) were added sequentially and stirred for 1 h. Extracted with ethyl acetate and washed with water, NaCl aq and dried (Na₂SO₄). Evaporation of the organic solvent and purification by flash column chromatography gave alcohol **133**.

¹H NMR (CDCl₃, 400 M Hz δ 6.91 (s, 1H); 6.44 (s, 1H); 5.17 (t, J = 6.4 Hz, 1HCH₂-); 4.18 (t, J = 6.2, 8 Hz, 1H); 3.5 (m, 2H), 2.7 (s, 3H), 2.25 (m, 2H), 1.9 (m, 5H), 1.66 (s, 3H); 1.4 (m, 2H); 0.92 (dJ =8 Hz, 3H); 0.88 (s, 9H); 0.004 (s, 3H); -0.005 (s, 3H).

Preparation of 134:

To a solution of compound **133** (437 mg, 1 mmol) in dichloromethane (10 ml), DMSO (1 ml) and Et₃N (0.5 ml, 5 mmol) Py•SO₃ complex (300 mg, 2 mmol) was added and allowed to stir at 25 °C for 2 h. Reaction mixture was quenched with NH₄Cl aq and extracted with diethyl ether (2x 25 ml). Combined organic layer was washed with water, NaCl aq and dried (Na₂SO₄). Organic solvent was removed under reduced pressure and flash chromatography purification afforded the aldehyde 201 mg (52%).

¹H NMR (CDCl₃, 400 M Hz δ 9.6 (d, J = 6 Hz, 1H), 6.92 (s, 1H); 6.44 (s, 1H); 5.16 (dd, J = 6.7, 6.4 Hz, 1H); 4.08 (t, J = 6.5, 5.1 Hz); 2.7 (s, 3H); 2.36 - 2.18 (m, 3H), 1.99 (s, 3H), 1.71-1.64 (m, 4H); 1.43 - 1.3 (m, 2H); 1.08 (d, J = 8Hz, 3H); 0.88 (s, 9H); 0.03 (s, 3H), -0.004 (s, 3H).

¹H NMR (CDCl₃, 400 M Hz δ

205, 164.4, 153.11, 142.3, 135.7, 122, 118.1, 114.8, 46.1, 25.7, 22, 18.6, 13.8, 13.2, -0.05. -0.01

Preparation of 124:

To a mixture of CuBr•DMS complex (4.1g, 20 mmol), ether (25 ml), dimethylsulfide (20 ml) at -45°C was added a 0.46 M solution of grignard (43.0 ml, 20.0 mmol) in ether over a period of 10 min. After 2h, propyne (1.1ml, 20.0 mmol) which has been condensed by

the cold finger at -45°C was added. The mixture was stirred at -23°C for 2.5 h and the resulting green solution was cooled to -78°C . A solution of 1-lithiopentyn [prepared from 20.0 mmol of pentyn and 20.0 mmol of n-BuLi in ether (20 ml)] and HMPA was transferred to the green solution. After 1h, epoxide (4.16g, 20.0 mmol) in ether (10 ml) was added over a 5 min period. The resulting mixture was stirred at -78°C for 3h and at -25°C for 24h. Quenched the reaction at 0°C by addition of saturated NH_4Cl solution (10 ml), adjusted the pH 8.0 with aqueous ammonia solution and partitioned between water and ether. The crude product was purified by flash column chromatography to yield (4.7g, 72%).

^1H NMR (400 MHz in CDCl_3) δ 5.16 (t, $J = 14.0$ Hz, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 3.78 (m, 1H), 3.48 (m, 1H), 2.07 (t, $J = 10$ Hz, 2H), 1.94 (m, 4H), 1.65 (s, 3H), 1.48 (m, 2H), 1.03 (d, $J = 8.0$ Hz, 3H), 0.82 (s, 9H), 0.006 (s, 3H), 0.00 (s, 3H).

To a solution of 124 (3.26g, 10.0 mmol) in dichloromethane (10 ml), 2,6-lutidine (1.28 ml) and TMSOTf (2.23 ml, 10.0 mmol) were added at 0°C . Reaction mixture was stirred at 0°C for 1h and aqueous NaHCO_3 solution was added. Extracted with ether (2 x 50 ml). Combined organic layer was washed with water, brine and dried over (Na_2SO_4). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **125** (3.78g, 95%).

^1H NMR (400 MHz in CDCl_3) δ 5.16 (t, $J = 8.0$ Hz, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 3.78 (m, 1H), 3.45 (m, 1H), 1.91 (m, 2H), 1.8 (m, 4H), 1.41 (m, 2H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.79 (s, 9H), -0.02 (s, 3H), -0.047(s, 3H).

Preparation of 126:

To a stirred solution of **125** (3.18g, 8.0 mmol) in THF (10 ml) at 25°C , (ipc) $_2\text{BH}$ (2.28g, 8.0 mmol) in THF was added. Reaction mixture was stirred at 25°C for 1h and quenched with NaOH and H_2O_2 (10.0 mmol each). Extracted with ether and washed with water, brine, dried over (Na_2SO_4). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave **126** (2.8g, 85%).

¹H NMR (400 MHz in CDCl₃) δ 5.11 (t, J = 8.2 Hz, 1H), 3.75 (m, 1H), 3.45 (m, 1H), 3.4 (m, 2H), 2.12 (m, 2H), 1.9 (m, 4H), 1.59 (s, 3H), 1.43 (m, 1H), 1.41 (m, 1H), 1.01 (d, J = 8.4 Hz, 3 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.79 (s, 9H), -0.015 (s, 3H), -0.046 (s, 3H).

Preparation of 100:

To a solution of (2.08g, 5.0 mmol) in CH₂Cl₂ (20 ml) and DMSO (2 ml) at 0°C, was added triethylamine ((2.0 ml) and SO₃•py complex (1.59g, 10.0 mmol) and the resulting mixture was stirred at 0°C for 90 min. Reaction mixture was quenched by addition of aqueous NH₄Cl (2.0 ml) and extracted with diethyl ether (2 x 25 ml). Combined organic extracts was washed with water, brine dried over (Na₂SO₄). Evaporation of the organic solvent and purification by flash column chromatography using silica gel gave aldehyde (1.73g, 84%).

¹H NMR (400 MHz in CDCl₃) δ 9.52 (s, 1H), 5.1 (t, J = 6.5 Hz, 1H), 3.5 (m, 1H), 3.29 (dt, J = 5.2, 4.0 Hz, 1H), 2.21 (dd, J = 4.8, 3.6 Hz, 2H), 2.08 (m, 1H), 1.94 (m, 2H), 1.61 (s, 3H), 1.32 (m, 2H), 1.01 (d, 6H), 0.79 (s, 9H), 0.065 (s, 3H), -0.025 (s, 3H).

Preparation of 135:

A solution of ketoacid **10** (69 mg, 0.028 mmol) in THF (2 ml) was added dropwise to a freshly prepared solution of LDA [prepared from diisopropylamine (57μL, 0.47 mmol) and n-BuLi (188 μL, 2.5 M solution in hexane, 0.47 mmol)] at -78°C. After being stirred for 15 min the solution was allowed to warm to -40°C, and after 30 min it was cooled to -78°C. A solution of aldehyde **134** (82 mg, 0.18 mmol) was added dropwise and the resulting mixture was stirred for 15 min and then quenched at -78°C by the slow addition of saturated aqueous NH₄Cl solution. The reaction mixture was warmed to 0°C and AcOH (0.2 ml) was added followed by the addition of EtOAc (5.0 ml). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 5 ml). The combined organic layer was dried over (Na₂SO₄). Evaporation of the organic solvent afforded a mixture of aldol products 1:1 ratio and the unreacted ketoacid. The mixture was dissolved in dichloromethane (2.0 ml) and treated at 0°C with 2,6-lutidine and tert.butyldimethylsilyl trifluoromethane sulfonate (0.42 ml, 0.18 mmol). After stirring for 2h aqueous HCl (10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with dichloromethane (3 x 5 ml) and the

combined organic phase was washed with brine, dried (Na₂SO₄) and concentrated under vacuum to give a mixture of tetra tert.butyldimethylsilyl ethers. The crude compound was dissolved in methanol (5 ml) and K₂CO₃ (140 mg, 0.1 mmol) was added at 25°C. The reaction mixture was vigorously stirred for 15 min and then filtered. The residue was washed with methanol (5 ml) and the solution was acidified with ion exchange resin (DOWEX 50 w x 8-200) to pH 4-5 and filtered again. The solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc and washed with saturated aqueous NH₄Cl solution (5.0 ml). The aqueous phase was extracted with EtOAc (4 x 5 ml) and combined organic layer was washed with brine, dried over (Na₂SO₄). Evaporation of the organic solvent and purification by thin layer chromatography gave **135** (22 mg).

¹H NMR (400 MHz in CDCl₃) δ 6.91 (s, 1H), 6.58 (s, 1H), 5.15 (dd, J = 7.4, 7.1 Hz, 1H), 4.6 (dd, 6.1, 5.2 Hz, 1H), 4.07 (m, 1H), 3.84 (dd, J = 7.0, 5.2 Hz, 1H), 3.11 (dq, J = 7.1, 6.5 Hz, 1H), 2.7 (s, 3H), 2.49 (m, 1H), 2.31 (m, 1H), 2.28-2.04 (m, 3H), 1.94 (s, 3H), 1.6 (s, 3H), 1.5 (m, 4H), 1.22 (s, 9H), 1.12 (s, 3H), 1.12 (m, 1H), 1.08 (d, J = 6.0 Hz, 3H), 0.9-0.85 (m, 30H), 0.111 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.043 (s, 3H), -0.003(s, 3H).

Preparation of 12Z-Hydroxy acid (136):

12Z-Carboxylic acid **135** (44mg, 0.047 mmol) was converted to 12Z-hydroxy acid **136** (21 mg) according to the same procedure described for compound **55**.

Macrolactonization of 136:

12Z-hydroxyacid was lactonized by using the same procedure outlined for the preparation for compound **46**.

Preparation of β-Lactone 155:

To a cooled solution of ketoacid **56** (364 mg or 2 mmol) in pyridine (3 mL) was added benzenesulfonyl chloride (528 mg or 3 mmol). The reaction mixture was stirred under argon at 0 °C for 1 h and at -22 °C for 12 h. Ether was added (100 mL) and the mixture washed with water (50 mL), 5% aq. CuSO₄ (50 mL), brine (50 mL) and the organic layer was then dried over Na₂SO₄. Filtration and rotary evaporation of solvent provided an oil which was purified by silica gel (240-400 mesh) flash chromatography to

give **155** as a colorless oil (221 mg or 70% yield). ^1H NMR (400 MHz, CDCl_3): δ 4.60 (t, $J = 5.6$ Hz, 1H), 3.46 (dd, $J = 6, 16$ Hz, 1H), 3.22 (dd, $J = 6, 16$ Hz, 1H), 2.52 (q, $J = 8, 12$ Hz, 2H), 1.25 (s, 3H), 1.18 (s, 3H), 1.0 (t, $J = 8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 213.4, 168.2, 74.6, 49.4, 40.0, 31.4, 20.4, 18.9, 8.0. IR (film), ν : 3022, 2976, 1831, 1705, 1634, 1467, 1333, 1126, 872, 756 cm^{-1} .

Preparation of Compound 167:

To a solution of compound **166** (6.64g, 20 mmol) in dichloromethane and diisopropylethylamine (3.8g, 30 mmol) trimethyl silyl ethoxy methyleneoxychloride (3.9g, 24 mmol) was added at 0 $^\circ\text{C}$. The mixture was stirred at room temperature for 6 h. The reaction was quenched with aq. ammonium chloride and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc to give the compound **167** (8.7g, 94%). ^1H NMR (400 MHz, CDCl_3): δ 7.26 (d, $J = 8$ Hz, 2H); 6.88 (d, $J = 8.1$ Hz, 2H); 5.13 (t, $J = 6.0$ Hz, 1H); 4.76 (s, 1H); 4.69 (s, 1H); 4.65 (dd, $J = 12$ Hz, 2H); 3.74 (dd, $J = 8$ Hz, 1H); 3.67 (m, 1H); 3.54 (dd, $J = 8.2$ Hz, 1H); 3.5 (s, 3H); 3.41 (m, 1H); 3.0 (d, $J = 6.0$ Hz, 1H); 2.5 (m, 2H); 2.1 (m, 6H); 1.69 (s, 3H); 1.68 (s, 3H); 1.5 (m, 2H); 0.9 (t, $J = 6.0$ Hz, 2H); 0.01 (s, 9H).

Preparation of Compound 168:

To a solution of compound **167** (8.7g, 18.8 mmol) in dichloromethane and water (80:20 ml) was added DDQ (3.9g, 20 mmol) at 0 $^\circ\text{C}$ and the reaction was stirred at room temperature for 2h. After completion of the reaction it was extracted with dichloromethane (50 ml x 3) and washed with aq. NaHCO_3 and brine solution. Organic phase was dried over Na_2SO_4 and evaporated under vacuo. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc to give product **168** (5.46g, 85%). ^1H NMR (400 MHz, CDCl_3): δ 5.15 (t, $J = 6.0$ Hz, 1H); 4.65 (s, 1H); 4.64 (s, 1H); 4.6 (dd, $J = 8.0$ Hz, 2H); 3.76 (dd, $J = 8.0$ Hz, 1H); 3.57 (m, 2H); 3.38 (m, 1H); 3.0 (d, $J = 6.0$ Hz, 1H); 2.34 (m, 1H), 2.3 (m, 1H); 2.02 (m, 6H); 1.72 (m, 2H); 1.69 (s, 3H); 1.68 (s, 3H); 1.4 (m, 2H); 0.9 (t, $J = 6.4$ Hz, 2H); 0.012 (s, 9H).

Preparation of Compound 169:

To a solution of SO₃.Py complex (4.044 g, 29 mmol), DMSO (4.6 ml, 60 mmol) and triethylamine (12.0 ml, 60 mmol) in dichloromethane (50 ml) was added compound 168 (5.1g, 14.49 mmol). The reaction mixture was stirred at room temperature for 8 h. Reaction was quenched with sat. ammonium chloride 10.0 ml and extracted with ethyl acetate (25 ml x 3). Combined organic extracts were dried over Na₂SO₄ and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc to give product **169** (3.8g, 78%). ¹H NMR (400 MHz, CDCl₃): δ 5.09 (t, J = 8.0 Hz, 1 H); 4.71 (dd, J = 8.4 Hz, 2H); 4.64 (s, 1H); 4.57 (s, 1H); 3.97 (t, J = 12.0 Hz, 1H); 3.64 (dd, J = 12.0 Hz, 2H); 2.35 (m, 2H); 2.1 (s, 3H); 1.93 (m, 4H); 1.64 (s, 3H); 1.62 (s, 3H); 1.48 (m, 2H); 0.9 (t, J = 8.0 Hz, 2H); 0.09 (s, 9H).

Preparation of Compound 170:

To a solution of compound **24** (3.5g, 14.0 mmol) in THF (30 ml) was added 2.5 M solution of n-BuLi (6.0 ml, 15 mmol in hexanes) at -78 °C. The solution was stirred for 1 h at that temperature. To this a solution of ketone **169** (3.8g, 11.2 mmol) in THF (20 ml) was added and the reaction mixture was brought to room temperature over a period of 12 h. The reaction was quenched with aq. ammonium chloride (10.0 ml) and extracted with ethyl acetate (25 ml x 3). Combined organic extracts were dried over Na₂SO₄ and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc to give product **170** (4.14g, 85%). ¹H NMR (400 MHz, CDCl₃): δ 6.94 (s, 1H); 6.48 (s, 1H); 5.18 (t, J = 8.2 Hz, 1H); 4.76 (s, 1H), 4.69 (s, 1H); 4.65 (dd, J = 12.0 Hz, 2H); 4.07 (t, J = 8.4 Hz, 1H); 3.77 (dd, J = 10.0 Hz, 1H); 3.52 (dd, J = 8.2 Hz, 1H); 2.7 (s, 3H); 2.36 (m, 1H); 2.34 (m, 1H); 2.03 (m, 4H); 2.0 (s, 3H); 1.69 (s, 3H); 1.68 (s, 3H); 1.5 (m, 2H); 0.93 (t, J = 6.0 Hz, 2H); -0.09 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 153.1, 137.8, 122.8, 121.6, 116.1, 110.1, 110.0, 92.4, 82.2, 65.5, 65.0, 38.0, 32.0, 26.3, 23.9, 22.8, 19.7, 18.5, 14.2, 0.1.

Preparation of Compound 171:

To solution of (IPC)₂BH (3.4g, 11.9 mmol) in THF (25 ml) was added a solution of compound **170** (4.14g, 9.5 mmol) in THF (25 ml). Reaction was stirred at room temperature for 0.5 h and water was added followed by the addition of saturated solution of sodiumperborate (5 ml) and LiOH (0.8g, 30 mmol). reaction was stirred at

room temperature for 2 h and extracted with ethyl acetate (25 ml x 3) and washed with brine solution. The combined organic extracts were dried over anhydrous Na₂SO₄ and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc to give product **171** (3.5g, 82%). ¹H NMR (400 MHz, CDCl₃): δ 6.94 (s, 1H); 6.48 (s, 1H); 5.18 (t, J = 6.0 Hz, 1H); 4.06 (dd, J = 8.6 Hz, 2H); 3.75 (dd, J = 8.4 Hz, 1H); 3.52 (m, 2H); 3.41 (dd, J = 6.0 Hz, 1H); 2.7 (s, 3H); 2.32 (m, 1H); 2.3 (m, 1H); 2.03 (m, 4H); 1.99 (s, 3H); 1.7 (m, 2H); 1.67 (s, 3H); 1.6 (m, 2H); 1.4 (m, 4H); 0.9 (t, J = 8 Hz, 2H); 0.89 (d, J = 8 Hz, 3H); 0.01 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 153.1, 137.7, 121.2, 116.2, 93.2, 77.1, 77.4, 72.2, 72.15, 67.4, 60.1, 37.1, 33.5, 32.3, 29.0, 19.5, 16.9, 15.2, 0.7, -0.09.

Preparation of Compound 172:

To a -78 °C cooled solution of oxalyl chloride (1.16g, 9.27 mmol) in dichloromethane (25 ml) was added DMSO (1 ml, 12 mmol) and stirred for 15 min. To this alcohol **171** (3.5g, 7.7 mmol) in dichloromethane (15 ml) was added and the reaction mixture was stirred at the same temperature for 1h. To this triethylamine (2.4g, 24 mmol) was added and the reaction mixture was warmed to 0 °C and quenched with water. Extracted with ether (25 ml x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and evaporated under vacuum. The crude product was purified by flash chromatography on silica gel using hexane/ether to give product **172** (3.05g, 88%). ¹H NMR (400 MHz, CDCl₃): δ 9.2 (d, J = 6.0 Hz, 1H); 6.95 (s, 1H); 6.49 (s, 1H); 5.18 (t, J = 8.0 Hz, 1H); 4.65 (dd, J = 8.2 Hz, 2H); 4.08 (t, J = 6.4 Hz, 1H); 3.74 (dd, J = 7.4 Hz, 1H); 3.52 (dd, J = 6.8 Hz, 1H); 2.7 (s, 3H); 2.32 (m, 1H); 2.3 (m, 1H); 2.01 (m, 4H); 2.0 (s, 3H); 1.72 (m, 2H); 1.68 (s, 3H); 1.6 (m, 2H); 1.54 (m, 1H); 1.2 (d, J = 8.2 Hz, 3H); 0.98 (t, J = 6.4 Hz, 2H); 0.009 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 175.8, 137.8, 121.7, 116.1, 110.0, 93.5, 77.8, 72.2, 67.2, 59.3, 36.1, 32.4, 25.6, 23.8, 19.5, 16.9, 14.2, 0.01, -0.09.

Aldol reaction:

A solution of ketoacid **10** (367mg, 1.12 mmol, 1.2 eq) in THF (4 ml) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (0.419 ml, 3 mmol) was added to n-BuLi (1.2 ml, 2.5 M solution in hexanes, 3.0 mmol) in 10 ml of THF at 0 °C] at -78 °C. After being stirred for 15 min, the solution was warmed to -40 °C, and after 0.5 h at

that temperature it was recooled to -78 °C. A solution of Zn Cl₂ (2.0 M solution in ether, 3.0 ml, 3 mmol) was added and stirred for 0.5 h, subsequently to this a solution of aldehyde **172** (451 mg, 1.0 mmol) in THF (5 ml) was added. The reaction mixture was stirred at this temperature for 0.5 h and warmed to -50 °C and stirred for an additional 0.5 h. Quenched the reaction with aq. ammonium chloride solution. Allowed to raised the temperature to 0 °C and acetic acid (6.0 eq) was added and extracted with ethyl acetate (25 ml x 3). The combined organic extracts were dried over anhydrous Na₂SO₄ and evaporated under vacuum to afford a mixture of aldol products **173a** and **173b**.

Epothilone B, 202:

[α]_D²⁵ -31 (c 0.25, CHCl₃)

IR(film): 3300(br), 2948, 2805, 1746, 1658, 1518, 1460, 1206, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 6.94(s, 1H); 6.59(s, 1H); 5.42(dd, J= 8.0, 3.0 Hz, 1H); 4.22(br, 2H); 3.71(t, J= 4.2 Hz, 1H); 3.29, (qd, J= 7.0, 4.2Hz, 1H); 2.8(dd, J= 7.5, 5Hz, 1H); 2.7(s, 3H); 2.65(br, 1H); 2.53(dd, J= 14.1, 10.2 Hz, 1H); 2.35(dd, J= 13.5, 2.5 Hz, 1H); 2.13(-2.06(m, 1H); 2.08(s, 3H); 1.91(dd, J= 15.6, 8.0 Hz, 1H); 1.77-1.65(m, 3H); 1.54-1.46(m, 2H); 1.45-1.35(m, 3H); 1.36(s, 3H); 1.27(s, 3H); 1.16(d, J= 7.0 Hz, 3H); 1.07(s, 3H); 0.99(d, J= 7.4 Hz, 3H). C¹³ (CDCl₃, 100 MHz) δ 220.7, 170.4, 165.0, 152.0, 139.2, 138.4, 120.9, 119.2, 115.6, 78.9, 74.1, 72.3, 53.5, 41.7, 39.6, 38.4, 32.5, 31.9, 31.7, 31.6, 25.4, 22.9, 19.0, 18.0, 15.9, 15.7, 13.4.

FAB HRMS *m/z* 508.2642, (MH)⁺ calcd for C₂₇H₄₁NO₆S 508.2655.

Epothilone D, 225:

[α]_D²⁵ -69.5 (c 0.27, CHCl₃)

IR(film): 3300(br), 2948, 2805, 1746, 1658, 1518, 1460, 1206, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 6.97(s, 1H); 6.61(s, 1H); 5.23(dd, J= 10.0, 6.0 Hz, 1H); 5.17(dd, J= 10.0, 4.0 Hz, 1H); 4.31(dd, J= 11.4, 6.0 Hz, 1H); 3.74(dd, J= 6.0, 4.0 Hz, 1H); 3.45(bs, 1H); 3.18(qd, J= 6.9, 2.8 Hz, 1H); 3.06(bs, 1H); 2.7(s, 3H); 2.63(dt, J= 15, 10, 1H); 2.48(dd, J= 14.6, 4.0 Hz, 1H); 2.36-2.29(m, 1H); 2.28(dd, J= 14.4, 3.0 Hz, 1H); 2.22(ddd, J= 15.6, 3.5, 2.0 Hz, 1H); 2.08(s, 3H); 1.91-1.88(m, 1H); 1.78-1.75(m, 2H); 1.68(s, 3H); 1.36(s, 3H); 1.33-1.24(m, 4H); 1.21(d, J= 8.0 Hz, 3H); 1.09(s, 3H); 1.05(d,

J= 9.0 Hz, 3H). C^{13} ($CDCl_3$, 100 MHz) δ 220.7, 170.4, 165.0, 152.0, 139.2, 138.4, 120.9, 119.2, 115.6, 78.9, 74.1, 72.3, 53.5, 41.7, 39.6, 38.4, 32.5, 31.9, 31.7, 31.6, 25.4, 22.9, 19.0, 18.0, 15.9, 15.7, 13.4.

FAB HRMS m/z 491.2601, $(MH)^+$ calcd for $C_{27}H_{41}NO_5S$ 491.2705.

7-TROC-Epothilone D, 224:

$[\alpha]^{25}_D$ -46.5 (c 1.5, $CHCl_3$)

IR(film): 3350(br), 2958, 2875, 1766, 1745, 1658, 1518, 1460, 1206, 915 cm^{-1}

H^1 NMR ($CDCl_3$, 400 MHz) δ 7.05(s, 1H); 6.73(s, 1H); 5.15(d, J= 10.0 Hz, 1H); 5.08(d, J= 8.0 Hz, 1H); 4.8(dd, J= 8.2, 3.0 Hz, 2H); 4.28(d, J= 8.0 Hz, 1H); 3.43(t, J= 6.0 Hz, 1H); 2.81(s, 3H); 2.7(d, J= 8.0 Hz, 1H); 2.68(d, J= 6.0 Hz, 1H); 2.52-2.49(m, 2H); 2.35(dd, J= 10.0, 2.0 Hz, 2H); 2.3(m, 1H); 2.2(dd, J= 6.0, 4.0 Hz, 1H); 2.07(s, 3H); 1.98(m, 2H); 1.65(s, 3H); 1.51(m, 2H); 1.39(s, 3H); 1.2(d, J= 8.0 Hz, 3H); 1.1(s, 3H); 1.03(d, J= 8.2 Hz, 3H). C^{13} ($CDCl_3$, 100 MHz) δ 217.2, 171.0, 166.0, 151.3, 142.6, 141.9, 141.1, 121.2, 120.0, 119.0, 89.1, 87.6, 83.1, 72.5, 54.3, 41.0, 37.1, 34.5, 31.5, 30.8, 28.6, 25.3, 23.1, 20.7, 16.2, 15.0, 14.6, 14.1, 10.6, 8.4.

FAB HRMS m/z 667.2642, $(MH)^+$ calcd for $C_{29}H_{41}Cl_3NO_6S$ 667.2655.

7-TROC-3-TBS-Epothilone D, 222:

$[\alpha]^{25}_D$ -49.8 (c 1.2, $CHCl_3$)

IR(film): 2948, 2805, 1759, 1746, 1658, 1518, 1460, 1206, 915 cm^{-1}

H^1 NMR ($CDCl_3$, 400 MHz) δ 6.99(s, 1H); 6.57(s, 1H); 5.21(dd, J= 10.0 Hz, 1H); 4.99(d, J= 11.2 Hz, 1H); 4.8(dd, J= 15.0, 10.2 Hz, 1H); 4.06(d, J= 10.2 Hz, 1H); 3.34(qd, J= 10.0, 3.5 Hz, 1H); 2.86(d, J= 15.0 Hz, 1H); 2.71(s, 3H); 2.69(d, J= 12.0 Hz, 1H); 2.54(t, J= 8.0 Hz, 1H); 2.13(s, 1H); 2.08-2.04(m, 2H); 1.8-1.76(m, 4H); 1.67(s, 3H); 1.61(m, 4H); 1.24(s, 3H); 1.21(s, 3H); 1.15(d, J= 11.0 Hz, 3H); 1.04(d, J= 10.0 Hz, 3H); 0.8(s, 9H); 0.15(s, 3H); -0.08(s, 3H). C^{13} ($CDCl_3$, 100 MHz) δ 217.0, 172.0, 166.7, 151.5, 142.0, 141.9, 141.8, 121.0, 120.2, 119.0, 89.1, 87.6, 83.1, 72.5, 54.3, 41.0, 37.1, 34.5, 31.5, 30.8, 28.6, 25.3, 23.1, 20.7, 16.2, 15.0, 14.6, 14.1, 10.8, 8.6, -6.2, -6.0.

FAB HRMS m/z 780.2601, $(MH)^+$ calcd for $C_{36}H_{56}Cl_3NO_7SSi$ 780.2612.

2S,6,10-Trimethyl-11-(2-methylthiazol-4-yl)-9S-(2-trimethylsilanyl-ethoxymethoxy)-undeca-6Z,10E -dien-1-al, 203:

$[\alpha]_D^{25}$ 12.1 (c 2.0, CHCl₃)

IR(film): 2908, 2858, 1716, 1658, 1518, 1465, 1256, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 9.5(d, J= 4.2 Hz, 1H), 6.93(s, 1H); 6.47(s, 1H); 5.18(t, J= 10.0 Hz, 1H); 4.63(dd, J= 12.0, 8.0 Hz, 2H); 4.06(t, J= 8.2 Hz, 1H); 3.75(q, J= 12.0, 8.4 Hz, 2H); 3.51(dd, J= 10.0, 8.0 Hz, 2H); 2.71(s, 3H); 2.31(m, 4H); 2.03(q, J= 10.0, 6.2 Hz, 2H); 1.99(s, 3H); 1.68(m, 2H); 1.66(s, 3H); 1.4(m, 4H); 1.35(m, 2H), 1.08(d, J= 12.0 Hz, 3H), 0.94(t, J= 8.4Hz, 2H); 0.002(s, 9H). ¹³C (CDCl₃, 100 MHz) δ 210.0, 161.07, 152.10, 139.19, 121.79, 121.65, 116.17, 92.52, 82.17, 65.61, 46.64, 33.08, 32.27, 30.72, 25.54, 23.83, 19.59, 18.50, 14.25, 13.30, -4.01.

FAB HRMS *m/z* 452.7368, (MH)⁺ calcd for C₂₄H₄₁NO₃SSi 452.7388

2S,6,10-Trimethyl-11-(2-methylthiazol-4-yl)-9S-(2-trimethylsilanyl-ethoxymethoxy)-undeca-6Z,10E -dien-1-ol, 216:

$[\alpha]_D^{25}$ 17.8 (c 1.2, CHCl₃)

IR(film): 3400(br), 2948, 2805, 1746, 1658, 1518, 1460, 1206, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 6.94(s, 1H); 6.48(s, 1H); 5.18(t, J= 8.0 Hz, 1H); 4.65(dd, J= 14.2, 8.0 Hz, 2H); 4.07(t, J= 8.0 Hz, 1H); 3.74(dd, J= 14, 8.2 Hz, 1H); 3.43(dq, J= 12.0, 8.2 Hz, 2H); 3.41(dd, J= 10.0, 8.4 Hz, 2H); 2.7(s, 3H); 2.31(m, 2H); 2.03(m, 2H); 1.99(s, 3H); 1.72(m, 2H); 1.67(s, 3H); 1.44(m, 2H); 1.37(m, 4H); 1.1(m, 2h); 0.95(t, J= 10.4 Hz, 2H); 0.89(d, J= 11 Hz, 3H); -0.09(s, 9H). ¹³C (CDCl₃, 100 MHz) δ 137.64, 121.63, 121.35, 115.20, 92.45, 85.74, 68.55, 65.53, 50.54, 34.7, 33.43, 32.54, 25.70, 24.12, 23.88, 19.52, 18.50, 16.95, 14.24, -4.01.

FAB HRMS *m/z* 454.2576, (MH)⁺ calcd for C₂₄H₄₁NO₃SSi 454.2675.

2-Methyl-4-[2,6,10-trimethyl-3-(2-trimethylsilanyl-ethoxymethoxy)-undeca-1,5,10-trienyl]-thiazole, 215:

$[\alpha]_D^{25}$ 18.4 (c 1.25, CHCl₃)

IR(film): 2948, 2805, 1658, 1518, 1480, 1460, 1206, 1165, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ 6.93(s, 1H); 6.48(s, 1H); 5.19(dd, J= 8.2, 6.0 Hz, 1H); 4.76(s, 1H); 4.65(dd, J= 12.2, 8.0 Hz, 2H); 4.09(t, J= 10.0 Hz, 1H); 3.72(q, J= 11.2, 6.0

Hz, 2H); 3.52(dd, J= 14.0, 10.4 Hz, 1H); 3.50(dd, J= 12.0, 6.0 Hz, 1H); 3.50(dd, J= 12.2, 8.2 Hz, 1H); 2.7(s, 3H); 2.36(dq, J= 10.1, 8.2 Hz, 1H); 2.31(dq, J= 10.0, 6.0 Hz, 1H); 2.04(m, 6H); 1.68(s, 3H); 1.66(s, 3H); 1.51(m, 4H); 0.9(t, J= 10.5, 2H); -0.09(s, 9H). C^{13} (CDCl₃, 100 MHz) δ 154.10, 146.41, 139.27, 137.55, 121.64, 121.36, 116.11, 110.17, 92.42, 82.27, 65.58, 38.09, 33.02, 32.05, 26.29, 23.89, 22.82, 19.60, 18.50, 14.22, -5.12

FAB HRMS m/z 436.2627, (MH)⁺ calcd for C₂₄H₄₁NO₂SSi 436.2637.

(2-{1-[1-(4-Methoxy-benzyloxy)-ethyl]-4,8-dimethyl-nona-3,8-dienyloxymethoxy}-ethyl)-trimethyl-silane, 212:

$[\alpha]_D^{25}$ 24.2 (c 2.5, CHCl₃)

IR(film): 2948, 2805, 1658, 1518, 1460, 1206, 1150, 915 cm⁻¹

H^1 NMR (CDCl₃, 400 MHz) δ 7.24(d, J= 12.0 Hz, 2H); 6.85(d, J= 11.4 Hz, 2H); 5.13(dd, J= 8.2 Hz, 1H); 4.77(s, 1H), 4.73(s, 1H); 4.69(dd, J= 12.0, 6.0 Hz, 2H); 4.48(dd, J= 6.4, 4.0 Hz, 2H); 3.81(s, 3H); 3.79-3.61(m, 3H); 2.2(m, 2H); 2.01(m, 4H); 1.7(s, 3H); 1.69(s, 3H); 1.54(m, 2H); 1.18(d, J= 10.4Hz, 3H); 0.93(t, J= 8Hz, 2H); 0.01(s, 9H). C^{13} (CDCl₃, 100 MHz) δ 156.21, 146.23, 137.44, 131.35, 129.52, 121.60, 119.69, 110.22, 110.0, 94.72, 79.46, 76.36, 70.89, 65.59, 55.64, 38.10, 32.03, 29.95, 26.25, 23.92, 18.50, 15.53, -4.12.

FAB HRMS m/z 449.2642, (MH)⁺ calcd for C₂₇H₄₇O₄Si 449.2655.

2-(4-Methoxy-benzyloxy)-6,10-dimethyl-undeca-5,10-dien-3-ol, 211:

$[\alpha]_D^{25}$ 21.8 (c 5.0, CHCl₃)

IR(film): 3415, 2968, 2845, 1658, 1518, 1460, 1206, 915 cm⁻¹

H^1 NMR (CDCl₃, 400 MHz) δ 7.26(d, J= 7.5 Hz, 2H); 6.78(d, J= 8.1Hz, 2H); 5.17(dd, J= 8.0, 4.0 Hz, 1H); 4.7(s, 3H); 4.67(s, 3H); 4.45(dd, J= 12.2, 6.0 Hz, 2H); 3.8(s, 3H); 3.71(m, 1H); 3.5(m, 1H); 2.18(m, 2H); 2.01(m, 4H); 1.71(s, 3H); 1.66(s, 3H); 1.26, m, 2H); 1.17(d, J= 6.9 Hz, 3H). C^{13} (CDCl₃, 100 MHz) δ 100.81, 95.40, 88.45, 81.13, 79.90, 71.93, 65.48, 61.76, 31.20, 30.96, 30.66, 27.53, 24.79, 10.57.

FAB HRMS m/z 333.2251, (MH)⁺ calcd for C₂₁H₃₂O₃ 333.2362.

2-[1-(4-Methoxy-benzyloxy)-ethyl]-oxirane, 205:

$[\alpha]_D^{25}$ 21.8 (*c* 5.0, CHCl₃)

IR(film): 2968, 1658, 1518, 1460, 1206, 1150, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ : 7.25(d, *J*= 8.4 Hz, 2H); 6.85(d, *J*= 8.2 Hz, 2H); 4.54(d, *J*= 12.0 Hz, 1H); 4.49(d, *J*= 12.2 Hz, 1H); 3.7(s, 3H); 3.39(dq, *J*= 8.4, 6.0 Hz, 1H); 2.91(m, 1H); 2.77(dd, *J*= 6.0, 4.0 Hz, 1H); 2.68(dd, *J*=6.6, 4.0 Hz, 1H); 1.28(d, *J*= 8.0 Hz, 3H).

¹³C(CDCl₃, 100MHz) δ 159.18, 132.1, 130.52, 129.06, 77.42, 73.91, 70.94, 55.14, 54.26, 45.64, 17.48

FAB HRMS *m/z* 209.1101, (MH)⁺ calcd for C₁₂H₁₆O₃ 209.1121.

Bromo-4-methyl-pent-4-ene, 209:

IR(film): 2968, 1658, 1518, 1460, , 1150, 915 cm⁻¹

¹H NMR (CDCl₃, 400 MHz) δ : 4.76(s, 1H); 4.72(s, 1H); 3.4(t, *J*= 8.0 Hz, 2H); 2.15(t, *J*= 6.2 Hz, 2H); 2.14(dd, *J*= 8.0, 4.0 Hz, 2H); 1.72(s, 3H). ¹³C (CDCl₃, 100 MHz) δ 144.31, 111.39, 36.49, 33.65, 30.99, 22.68.

FAB HRMS *m/z* 163.0004, (MH)⁺ calcd for C₆H₁₁Br 162.0104

Accordingly, the present invention has been described with some degree of particularity directed to the exemplary embodiments of the present invention. It should be appreciated, though, that the present invention is defined by the following claims construed in light of the prior art so that modifications or changes may be made to the exemplary embodiments of the present invention without departing from the inventive concepts contained herein.